Cardiovascular System (CVS)

(CARDIOLOGY)

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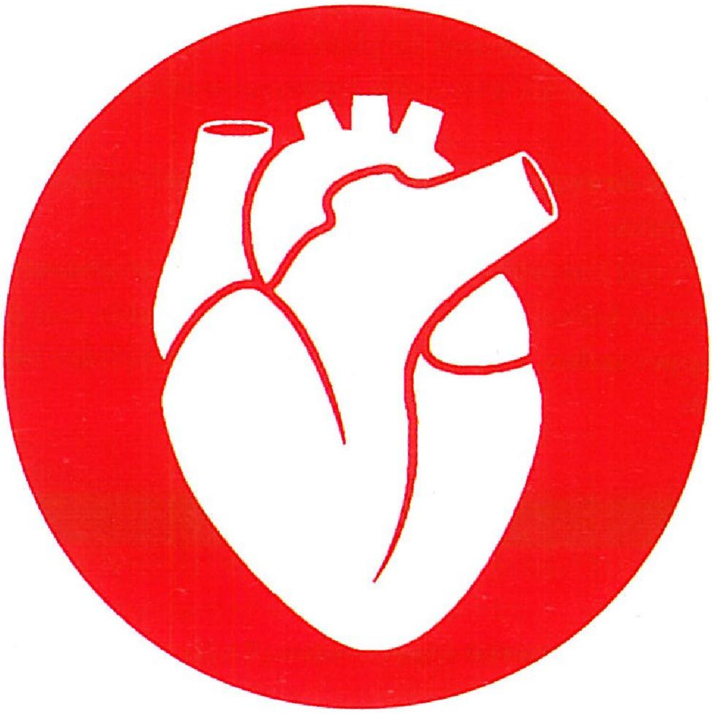
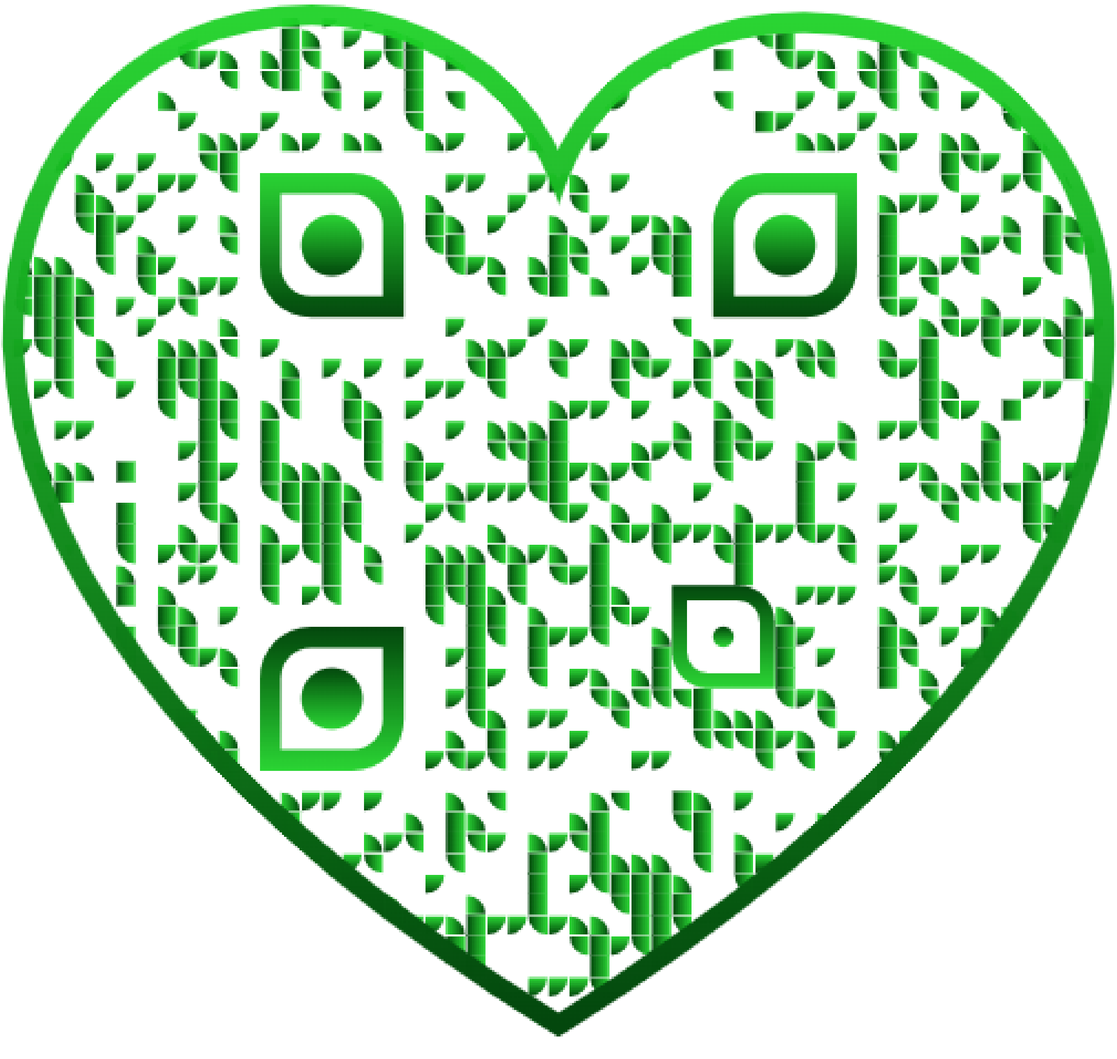




Hypertension

Definition:-

- **Hypertension** (**HTN** or **HT**), *also known as* **high blood pressure** or **arterial hypertension**; is a chronic condition in which the blood pressure (BP) in the arteries is persistently elevated.
- ***Simply***; **Hypertension** is considered a blood pressure (BP) of 140/90 mm Hg or higher.

Background:-

- Most common chronic disease in the United States.
- Affects about 78 million Americans (*American Heart Association* report; 2013).
- Major modifiable risk factor for CV disease and stroke.
- HTN is adequately controlled in only 52.5% of patients with HTN.

Normal Regulation of Blood Pressure:-

- **Arterial blood pressure** is ***directly proportionate*** to the product of the **blood flow** (cardiac output; CO) and the **resistance** to passage of blood through arterioles (peripheral vascular resistance; PVR), i.e. **BP**; is a pressure generated when the heart pumps the blood against the resistance of arterioles.

BP = Cardiac Output (CO) X Peripheral Vascular Resistance (PVR)

- **Cardiac Output (CO)**: **CO** = Stroke Volume (**SV**) **X** Heart Rate (**HR**)
- **Stroke Volume (SV)**: is the volume of blood pumped from the left ventricle of the heart per beat.
- **Heart Rate (HR)**: is the speed of the heartbeat measured by the number of poundings of the heart per unit of time (typically beats per minute).

- ***Increase*** CO or PVR, or both ⇨ ***Increase*** BP.
- ***Decrease*** CO or PVR, or both ⇨ ***Decrease*** BP.

- In ***both*** **normal** and **hypertensive individuals**, BP is maintained by **moment-to-moment regulation** of CO and PVR, ***through***;
  - **Neural *Mechanisms***: baroreceptors and autonomic nervous system.
  - **Renal *Mechanisms***: renin-angiotensin-aldosterone system and aldosterone.
  - **Local Endothelium-Derived *Factors***: nitric oxide (VD) and endothelin (VC).
  - **Other *Hormones***: e.g.; natriuretic peptides, vasopressin & kallikrein-Kinin system.

Uncontrolled Hypertension Effects on the Body:-

Arteries Damage;
- Artery walls thick and stiff (**arteriosclerosis**).
- ***Cause***; angina (chest pain), heart attack, heart failure, kidney failure, stroke, blocked arteries in legs or arms (peripheral artery disease) and eye damage.

Heart Damage;
- Uncontrolled high blood pressure can damage the heart in a number of ways, such as: **coronary artery disease**, **enlarged left heart** (left ventricular hypertrophy) and **heart failure** (heart muscle weakness and work less efficiently).

Kidneys Damage;
- Uncontrolled high blood pressure can injure renal blood vessels and leading **nephropathy**.
- ***Cause***, weakens and damages the artery wall, lead to kidney failure.
- Diabetes in addition to high blood pressure can worsen the damage.

Eye Damage;
- *Cause*; **Hypertensive Retinopathy**:
  - Damage in the arterial and arteriolar circulation in response to the high blood pressure.

Brain Damage;
- **Stroke**; due to damaging and weakening brain blood vessels.
- **Dementia;** due to narrowing and blockage of the arteries that supply blood to the brain.

➢ Some of Medical Terms:-

- **Systolic Blood Pressure (SBP)**;
  is the **top number**, the ***highest pressure*** when the heart pushes the blood into the body.
- **Diastolic Blood Pressure (DBP)**;
  is the **bottom number**, the ***lowest pressure*** when the heart relaxes between beats.
- **Mean Arterial Pressure (MAP)**; is the average over a cardiac cycle and is determined by the cardiac output, systemic vascular resistance and central venous pressure.

Typically more attention is given to the top number (SBP) as a major risk factor, due to increasing stiffness of large arteries, long-term build-up of plaque, and increased incidence of cardiac and vascular disease.

➢ Normal Resting Blood Pressure by Age:-

Blood Pressure Value	Male Age (year)			Female Age (year)		
	10-15	20-30	50-60	10-15	20-30	50-60
Systolic blood pressure SBP (mmHg)	100	120	134	84	120	130
Diastolic blood pressure DBP (mmHg)	60	80	84	40	74	84
Mean arterial pressure MAP (mmHg)	73	93	97	55	88	92

➢ Classification of Hypertension Defined by the American Heart Association:-

Blood Pressure Category	Systolic (mmHg)		Diastolic (mmHg)	Follow-up and Notes
Normal	< 120	and	< 80	- Yearly checks. - Healthy lifestyle choice.
Elevate Blood Pressure	120-129	and	< 80	- Reassessed in 3-6 months. - Healthy lifestyle modifications.
Stage 1	130-139	or	80-89	- Reassessed in 3-6 months. - Monthly follow-up until BP is controlled. - 10-year heart disease and stroke risk assessment. - Healthy lifestyle modifications.
Stage 2	≥ 140	or	≥ 90	- Monthly follow-up until BP is controlled. - Healthy lifestyle modifications. - 2 different classes of medicine.
Hypertensive Crisis	> 180	and/or	> 120	- Emergency care needed

R; American Heart Association *New* Guidelines (Published; Nov, 13, 2017).

➢ Benefits of Lowering Blood Pressure:-

- ***Decreased*** **risk** of **stroke** (by 40%).
- ***Decreased*** **risk** of **myocardial infarction** (MI) (by 25%).
- ***Decreased*** **risk** of **heart failure** (HF) (by 50%).

➢ Classification of Hypertension Defined by Causes:-

- **Primary (Essential or Idiopathic) Hypertension**:
  - The majority of cases about 90% (no identifiable causes).
  - No specific medical causes.
  - Unknown etiology but multiple factors may contribute to the development of primary hypertension including;
    - Smoking, obesity, stressful lifestyle, high dietary intake of sodium, family history and alcohol intake.
    - Overactive of renin-angiotensin system or sympathetic nervous system.
    - Deficiency in the local synthesis of vasodilating substances (NO, bradykinin and prostacyclin) or excess vasoconstricting substances (angiotensin II and endothelin).
    - Insulin resistance, hyperinsulinemia and obesity, also linked with renin-angiotensin system.
    - Vitamin D deficiency may leads to an increase in renin secretion.
  - Prevalence of essential hypertension increases with age.

- **Secondary Hypertension**:
  - Few cases about 10%.
  - Most of these are caused by ↘
    - Chronic kidney disease or renovascular disease.
    - Primary aldosteronism (Conn's syndrome) & hypercortisolism (Cushing's syndrome).
    - Pheochromocytoma and hyperthyroidism.
    - Drugs that may increase BP include;
      - Corticosteroids, Estrogens, NSAIDs and Amphetamines.

➢ Causes of Hypertension:-

Nature causes	Chemical causes
- Genetics. - Salt sensitivity. - Obstructive sleep apnea (OSA). - Insulin resistance and hyperinsulinemia. - Stressful situations, obesity, smoking and other lifestyle. - Kidney problems. - ***Endocrine causes:*** o Primary aldosteronism. o Pheochromocytoma. o Hyperthyroidism. o Cushing's syndrome.	- Salts. - Alcohol. - Oral contraceptives. - NSAIDs. - ***Glycyrrhiza glabra*** (Liquorice). - Decongestants. - Antidepressants. - Sympathomimetics. - Many industrial chemical. - Corticosteroids. - Ergotamine alkaloids. - Cyclosporine (Immunosuppressant drug). - Cocaine. - Caffeine.

➢ Clinical Presentation:-

- Patients with uncomplicated primary hypertension are usually asymptomatic initially.
- Patients with secondary hypertension may have symptoms suggestive of the underlying disorder;
  - ***Pheochromocytoma***; sweating, tachycardia and palpitations.
  - ***Primary aldosteronism***; hypokalemia symptoms (muscle cramps & weakness).
  - ***Cushing's syndrome***; weight gain, polyuria, edema, moon face and buffalo hump.
    - *N.B; **Primary aldosteronism** and **Cushing's syndrome** see endocrine chapter.*

➢ Hypertension Risk Factors :-

- **Risk factors that can be controlled are:**
  - High cholesterol level.
  - Tobacco use (smoking).
  - Diabetes mellitus.
  - Overweight and obesity.
  - Physical inactivity.
  - High salt intake.
  - Coarctation of the aorta.
  - Sleep apnea.
- **Risk factors beyond our control are:**
  - Age.
  - Family history of heart disease.

➢ Diagnosis of Hypertension:-

- **NO** *Smoking*, **NO** *Exercise* and **NO** *Coffee*; **30 minutes** *before* **BP** is *taken*.
- **Patient** ***should be*** **seated quietly** *in* **chair** ***for at least* 5 minutes** (**NO** *taking*).
- **Reading** ***should be*** based on the **average of** ***two*** **or** ***more*** **readings taken at each** *of* **two** *or* **more clinical encounters.**
- **Hypertension** progress may lead to serious ***complications***, some of **clinical diagnosis** is needed;
  - **Funduscopic examination** (*examination of the eye*).
  - **Cardiopulmonary examination.**
  - **Peripheral vascular examination.**
  - *Laboratory tests*;
    - **Plasma electrolytes**; hypokalemia may suggest primary aldosteronism.
    - **Urine analysis**; proteins, blood cells and casts in the urine may indicate renovascular disease.
    - **Blood urea nitrogen** (**BUN**) **to creatinine ratio** and **glomerular filtration rate** (**GRF**) also be obtained.
    - **Lipid profile** and **blood glucose level**.
    - **Plasma norepinephrine** and **urinary metanephrine** or **vanillylmandelic acid** (**VMA**) level for pheochromocytoma.
    - **Plasma and urinary aldosterone** level for primary aldosteronism.

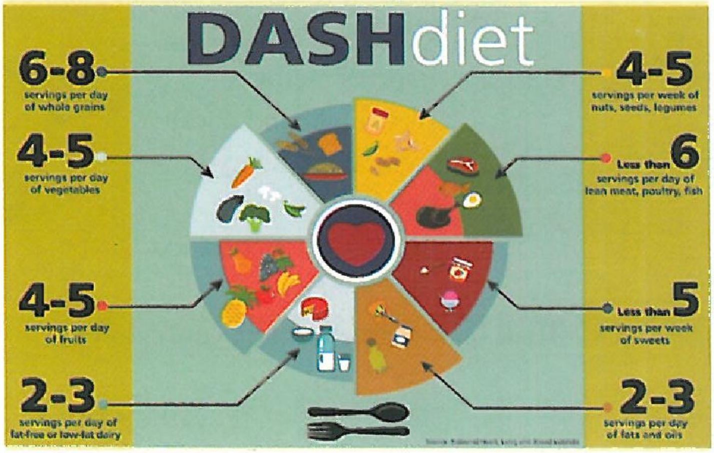
➢ Treatments of Hypertension :-

Lifestyle Modification (Non-pharmacologic treatments)	Medications (Antihypertensive drugs)
- **DASH eating plan** (*See below*):	- Diuretics.
- *BP reduced by 8–14 mm Hg.*	- β-blockers (BBs).
- **Dietary sodium** (salts) **restriction**:	- ACE Inhibitors (ACEIs).
- *BP reduced by 2–8 mm Hg.*	- Angiotensin Receptor Blockers (ARBs).
- **Weight loss**; Normal weight (BMI 18.5–24.9 kg/m2)	- Direct Renin Inhibitors.
- *BP reduced by 5–20 mm Hg per 10-kg weight loss.*	- α-blockers.
- **Regular aerobic physical activity**:	- Calcium Channel Blockers (CCBs).
- *BP reduced by 2–9 mm Hg.*	- Centrally Acting Sympathetic Inhibitors.
- **Moderate alcohol consumption**:	- Peripherally Acting Sympathetic Inhibitors
- *BP reduced by 2–4 mm Hg.*	- Ganglionic Blockers.
- **Smoking cessation.**	- Vasodilators.
- **Reduction of environmental stressors.**	- Natural Antihypertensive Agents.

* **Lifestyle modification** ***alone*** **are effective for most patients with prehypertension,** ***but*** is **insufficient alone for patients with hypertension.**

➢ Dietary Approaches to Stop Hypertension (DASH) Eating Plan:-

- **Is a diet that is low in;** Saturated fats and cholesterol.
- **It encourages fewer servings of;** Limits sodium (2,300 mg of sodium a day), sweets, sugary beverages and red meats.
- **It also includes:** Vegetables, fruits, and fat-free or low-fat dairy products.
- **It is rich in:** Magnesium, potassium, calcium, as well as proteins and fibers.


DASHdiet
6-8 servings per day of whole grains
4-5 servings per day of vegetables
4-5 servings per day of fruits
2-3 servings per day of fat-free or low-fat dairy
4-5 servings per week of nuts, seeds, legumes
Less than 6 servings per day of lean meat, poultry, fish
Less than 5 servings per week of sweets
2-3 servings per day of fats and oils

Antihypertensive Drugs

1) Diuretics

- **Diuretics**, sometimes *called* **water pills**, treat a variety of conditions, such as **high blood pressure**, **glaucoma** and **edema**.
- **Diuretics** *are* **drugs** that *increase* **urine volume** by *promoting* the **excretion of salt and water** from the kidneys.

➢ Classification of Diuretics :-

- **Extra-renal** (**Pre-renal**):
  - **Water** and **Ethyl alcohol**; ↓ ADH release ⇨ ↓ water reabsorption.
  - **Digitalis** ***only*** in **heart failure**; +ve inotropic ⇨ ↑ CO ⇨ ↑ renal blood flow.
  - **Albumin** ***only*** in **hypoalbuminemia**; restore osmotic pressure ⇨ ↑ blood volume.
  - **Dobutamine and Dopamine**; ↑ CO ⇨ ↑ renal blood flow. (Dopamine; renal VD).
  - **Methylxanthines e.g. Theophylline**; ↑ CO and renal VD ⇨ ↑ renal blood flow.
- **Renal**:

  A) Saluretics (facilitating the urinary excretion of salt; especially Na^+):
  - ***High efficacy*** (**high ceiling**); **loop diuretics** e.g. **Furosemide**.
  - ***Moderate efficacy***; **thiazide diuretics** e.g. **Hydrochlorothiazide** (**HCTZ**).
  - ***Low efficacy***;
    - **Potassium** (K^+) **sparing diuretics** e.g. **Spironolactone** and **Triamterene**.
    - **Carbonic anhydrase inhibitors** e.g. **Acetazolamide**.

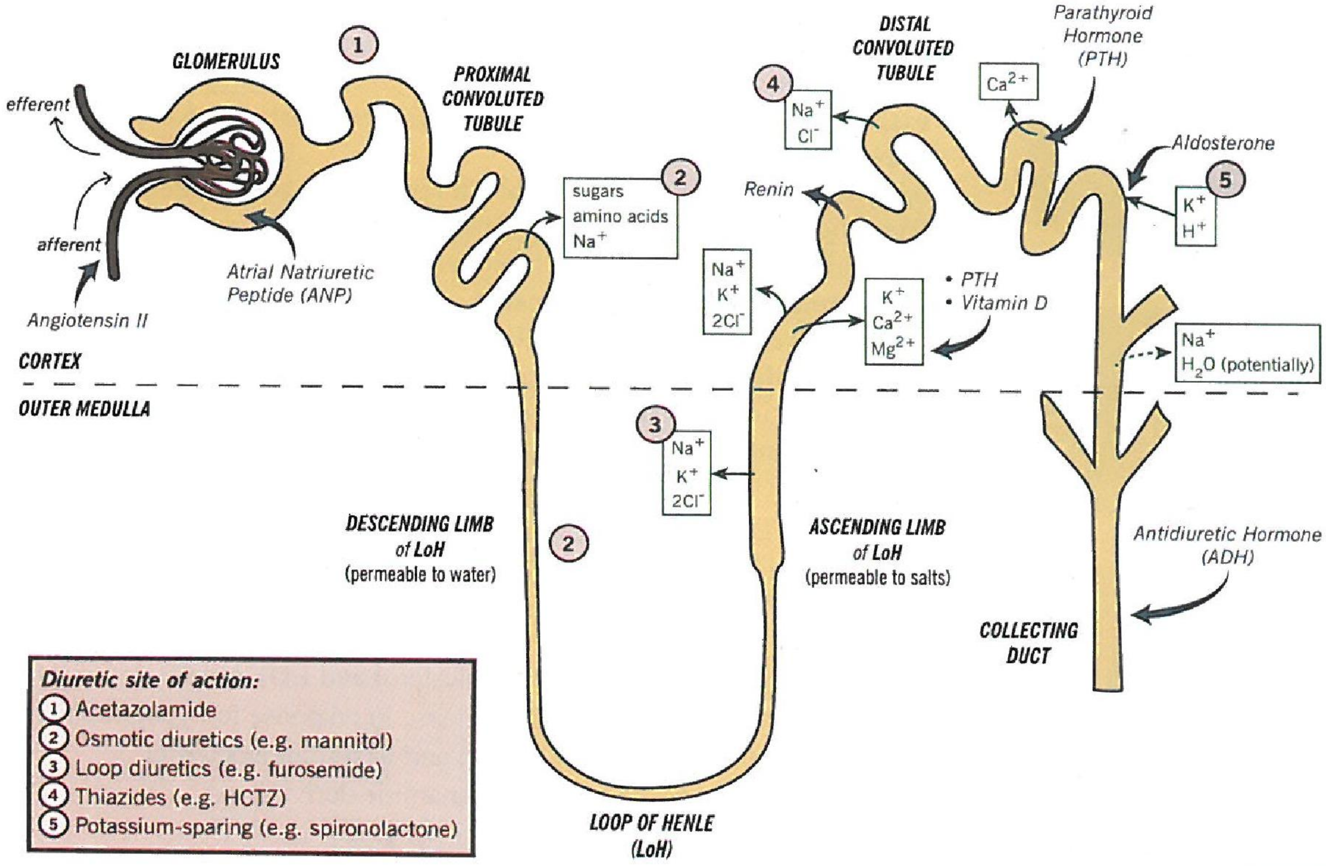
  B) Osmotic diuretics e.g. **Mannitol**.

  C) Acidifying diuretics e.g. **Ammonium Chloride** (NH_4Cl).

➢ Diuretics Used in High Blood Pressure:-

- There are **three types of diuretics** *used in* **high blood pressure**: **thiazide**, **loop** and **potassium-sparing**. Each works by affecting a different part of the kidneys, and each may have different uses, side effects and precautions.

➢ Diuretics and Their Site of Action:-


GLOMERULUS
①
PROXIMAL CONVOLUTED TUBULE
efferent
afferent
Angiotensin II
Atrial Natriuretic Peptide (ANP)
CORTEX
OUTER MEDULLA
②
sugars
amino acids
Na+
DISTAL CONVOLUTED TUBULE
Parathyroid Hormone (PTH)
Ca2+
④
Na+
Cl-
Renin
Aldosterone
⑤
K+
H+
Na+
K+
2Cl-
K+
Ca2+
Mg2+
• PTH
• Vitamin D
Na+
H2O (potentially)
③
Na+
K+
2Cl-
DESCENDING LIMB of LoH (permeable to water)
②
ASCENDING LIMB of LoH (permeable to salts)
Antidiuretic Hormone (ADH)
COLLECTING DUCT
LOOP OF HENLE (LoH)
Diuretic site of action:
① Acetazolamide
② Osmotic diuretics (e.g. mannitol)
③ Loop diuretics (e.g. furosemide)
④ Thiazides (e.g. HCTZ)
⑤ Potassium-sparing (e.g. spironolactone)

➢ Major segments of the nephron and their function:-

Segment	Function	Water permeability	Diuretic with major action
Glomerulus	- Formation of glomerular filtrate	Extremely high	None
Proximal convoluted tubule (PCT)	- Reabsorption of 65% of filtered Na$^+$, K$^+$, Ca^{2+} & Mg^{2+}. - Reabsorption of 85% of $NaHCO_3$. - Reabsorption of 100% of glucose and amino acids.	Very high	Carbonic anhydrase inhibitors
Thin descending limb of Henle's loop	- Passive reabsorption of water.	High	None
Thick ascending limb of Henle's loop (TAL)	- Active reabsorption of 15-25% of filtered Na$^+$, K$^+$ & Cl$^-$. - Secondary reabsorption of Ca^{2+} and Mg^{2+}.	Low	Loop diuretics
Distal convoluted tubule (DCT)	- Active reabsorption of 4-8% of filtered Na$^+$ & Cl$^-$. - Ca^{2+} reabsorption under parathyroid hormone control.	Very low	Thiazides
Cortical collecting tubule (CCT)	- Na$^+$ reabsorption (2-5%) coupled to K+ and H$^+$ secretion.	Variable	K$^+$-sparing diuretics

➢ Action of Diuretics:-

- *Initially*; diuretics reduce blood pressure by reducing blood volume and cardiac output; peripheral vascular resistance may increase. ***After*** 6-8 weeks; cardiac output returns toward normal while peripheral vascular resistance declines.
- **Diuretics** are ***effective*** in **lowering blood pressure** by **10-15 mm Hg** in most patients.

Thiazide Diuretics (Low Ceiling)

- Thiazide is a type of molecule and a class of diuretics often used to treat hypertension and edema.
- In most countries, the thiazides are the cheapest antihypertensive drugs available.

Hydrochlorothiazide (HCTZ, HCT or HZT) (Esidrix®)	Chlortalidone or Chlorthalidone (Thalitone®)

- Thiazide diuretics *such as* **hydrochlorothiazide** [hye-droe-klor-oh-THYE-a-zide] & **chlorthalidone** [klor-THAL-ih-done], lower blood pressure ***initially*** by ***increasing*** **sodium and water excretion.**
- **Thiazide diuretics** are ***useful*** in **combination therapy** with a variety of other antihypertensive agents, including β-blockers, ACE inhibitors, ARBs, and potassium-sparing diuretics.
- **Thiazide diuretics** are ***not effective*** in **patients with inadequate kidney function** (estimated glomerular filtration rate less than 30 mL/min/m^2). **Loop diuretics** may be required in these patients.
- ***Dose***; **Hydrochlorothiazide**; 25-100 mg/day (single dose). **Chlorthalidone**; 25-50 mg/day (single).

Mechanism OF Action

- ***Decrease*** **blood pressure** by ***increasing*** **sodium** and **water excretion** by ***reducing*** **reabsorption** of **sodium** and **chloride** at the **early part of the distal convoluted tubule** in the nephrons. **Resulting** in ***decrease*** **extracellular volume**, ***decrease*** **cardiac output** ⇨ ***decrease*** **blood pressure.**
- ***Increase*** the **reabsorption of Ca^{2+}** in response to sodium depletion.
- The action of thiazides depends in part on renal prostaglandin production. The action of thiazides can be inhibited by NSAIDs in certain conditions.

Therapeutic Uses

1) **Mild and moderate hypertension.**
2) **Congestive heart failure (CHF)**; due to ↓ preload & afterload in heart.
3) **Nephrolithiasis (Idiopathic hypercalciuria)**; *Preventing* calcium-containing kidney stones, ***useful in*** **hypocalcemia** and **osteoporosis.**
4) **Nephrogenic diabetes insipidus**; The evidence suggests the anti-diuretic effects of thiazides in nephrogenic diabetes insipidus is intimately related to depletion of body sodium or due to decrease GFR.

Side Effects

- **Hypokalemia** and **metabolic alkalosis**; *due to* ↑ secretion of K$^+$ & H$^+$.
- **Hypercalcaemia**; *due to* ↑ reabsorption of Ca^{2+}.
- **Hyperuricemia**; *due to* ↑ reabsorption of uric acid, due to hypovolemia.
- **Hyperlipidemia**; *due to* ↑ total cholesterol and LDL level.
- **Hyperglycemia**; *due to* ↓ insulin release in response to hypokalemia.
- **Hyponatremia** (↓ Na$^+$ in the blood) and **hypomagnesaemia.**
- **Hypersensitivity** (thiazides are sulfonamide derivatives).

Contra indication

- **Digitalis toxicity**; hypokalemia & hypercalcaemia worsen these toxicity.
- **Hepatic cirrhosis** (overzealous use) and **renal failure**.
- **Patients with a history of sulfonamide allergy.**
- **Gout**; *due to* hyperuricemia.
- **Diabetes mellitus**; *due to* hyperglycemia.

Drug Interactions

- **Lithium**; *due to* ↓ renal lithium excretion.
- **Digitalis**; *due to* ↑ digitalis toxicity.
- **NSAIDs**; *due to* ↓ diuretic effect of thiazide.

Thiazide-Like Diuretics (Thiazide Analogues)

Indapamide (Natrilix® SR)

- **Indapamide** [in-DAP-a-mide] is the ***first*** of a ***new class*** of '**antihypertensive/diuretics**'.
- It have a **unique mechanism of action**; act by combining **diuretic effects *with* a direct vasodilatation** (Ca^{2+} channels blocker) **effect**.
- It ***used*** in **hypertension** and **edema** *due to* **congestive heart failure**.
- ***Dose***; 2.5-10 mg/day (single dose).
- The drug produces toxicity similar to that of the thiazide diuretics.

Clopamide (Hypoten®) | Xipamide (Epitens®) | Metolazone (Zaroxolyn®)

- **Clopamide** [kloe-pa-myde], **Xipamide** [Zee-pah-mide] and **Metolazone** [meh-TOLE-uh-ZONE] are a thiazide-like diuretic and works in similar way as the thiazide diuretics.

Loop Diuretics (High Ceiling)

- **Loop diuretics** are the ***most efficacious*** **diuretic agents currently available.**
- **Loop diuretics** are ***more effective*** in **patients with impaired kidney function**.

Furosemide (Lasix®) | Torsemide (Examide®) | Bumetanide (Burinex®) | Ethacrynic acid (Edecrin®)

- **Furosemide** [fur-OH-se-mide], **Torsemide** [TORE-se-mide], **Bumetanide** [byoo-MET-a-nide] are sulfonamide loop diuretics. **Ethacrynic acid** [eth-a-KRIN-ik AS-id], not a sulfonamide diuretics.

Pharmaco Kinetics

- ***Absorption***; absorption of oral **torsemide** is ***more rapid*** (1 hour) than that of **furosemide** (2-3 hours).
- ***Duration of action***; **Furosemide** ⇨ 2-3 hours, **Torsemide** ⇨ 4-6 hours.

Drug	Total daily dose	Relative potency
Furosemide	20-80 mg	1
Torsemide	5-20 mg	3
Bumetanide	0.5-2 mg	40
Ethacrynic acid	50-200 mg	0.7

Mechanism OF Action

- ***Decrease*** blood pressure by ***increasing*** sodium and water excretion by ***reducing*** reabsorption of Na$^+$, K$^+$ & Cl$^-$ at the **thick ascending limb of Henle's loop (TAL)** in the nephrons.
- ***Decrease*** renal vascular resistance and ***increase*** renal blood flow via ***increase*** the **production** of **vasodilator prostaglandins**, so NSAIDs can reduce the efficacy of loop diuretics.

Therapeutic Uses

1) **Edema**; ***caused by*** **congestive heart failure**, it is also used for **hepatic cirrhosis, renal impairment, nephrotic syndrome**, in adjunct therapy for **cerebral** or **pulmonary edema**.
2) **Hypertension**; ***Oral***; used in adults for **hypertension *alone*** or in ***combination***. ***IV***; used in **emergency hypertension**.
3) **Oliguria** (< 400 ml urine/day); ***Use only*** **high dose tablet (Furosemide 500 mg)** or **injection (Furosemide 250 mg)** in the treatment of oliguria *due to* acute or chronic renal failure with a glomerular filtration rate (GFR) of below 20mL/min.
4) **Other non-specific uses; Hyperkalemia**.

Side Effects

- **Hypokalemia** and **metabolic alkalosis**; *due to* ↑ secretion of K^+ & H^+.
- **Ototoxicity** (toxic to the ear *or* deafness); loop diuretics occasionally cause dose-related hearing loss that is usually reversible, most common in patients who have diminished renal function or who are also receiving other ototoxic agents such as aminoglycosides antibiotics.
- **Hyperuricemia**; *due to* ↑ reabsorption of uric acid, due to hypovolemia.
- **Hypomagnesaemia**; *only* in chronic uses.
- **Hyponatremia**; *less common* than thiazides, ***but*** patients who increase water intake in response to hypovolemia-induced thirst can become severely hyponatremic with loop agents.
- **Severe dehydration**.
- **Hyperlipidemia**; *less common* than thiazides.
- **Hyperglycemia**; *less common* than thiazides.
- **Hypersensitivity**; especially with sulfonamide loop diuretics (furosemide torsemide and bumetanide).
- **Ca^{2+} balance remain neutral**, loop diuretics cause an increase in renal calcium excretion, this appears to be compensated for by a parathyroid-dependent increase in vitamin D levels, which increases intestinal calcium absorption, may lead to mild hypocalcemia and secondary hyperparathyroidism.

Contra indication

- **Digitalis toxicity**; hypokalemia worsen these toxicity.
- **Hepatic cirrhosis** (overzealous use).
- **Patients with a history of sulfonamide allergy**.
- **Gout**; *due to* hyperuricemia.

Drug Interactions

- **Aminoglycosides antibiotics**; ↑ ototoxicity.
- **Lithium**; *due to* ↓ renal lithium excretion.
- **Digitalis**; *due to* ↑ digitalis toxicity.
- **NSAIDs**; *due to* ↓ diuretic effect of loop diuretics.
- **Warfarin**; furosemide displace warfarin from plasma protein binding site.
- **Probenecid**; *due to* ↓ renal tubular excretion of furosemide.

Potassium (K^+) Sparing Diuretics

- **Potassium-sparing diuretics *prevent* K^+ secretion** by antagonizing the effects of aldosterone in collecting tubules (aldosterone antagonists) ***or*** by inhibition of Na^+ influx through ion channels in the luminal membrane (non-aldosterone antagonists).

Aldosterone Antagonists

Spironolactone (Aldactone®)	**Eplerenone** (Inspra®)

- **Spironolactone** [speer-on-oh-LAK-tone] is a synthetic steroid that acts as a competitive antagonist to aldosterone at mineralocorticoid receptors, it has a slow onset of action requiring several days before full therapeutic effect is achieved.
- **Eplerenone** [eh-PLEH-reh-none] is a spironolactone analogue with much greater selectivity for the mineralocorticoid receptors.
- **Eplerenone** has a several hundredfold less active on androgen and progesterone receptors than **Spironolactone**, therefore, **Eplerenone** has considerably fewer adverse effects.

Mechanism OF Action

- ***Inhibits*** the **effects** of **aldosterone**, by **competitive antagonist** at **mineralocorticoid receptors** at the aldosterone-dependent Na^+-K^+ exchange site in the **distal convoluted renal tubule** ⇨ ↑ Na^+ and water excretion, *while* K^+ is retained, H^+ excretion is decreased (Acidosis).
- Spironolactone has ***other effects*** e.g.; **antiglucocorticoidic** (Inhibit production of the glucocorticoid hormones), **antiandrogenic** (block androgen receptor), **progestogenic** & **estrogenic effects**.

Therapeutic Uses

- **Spironolactone** ***uses***;
  - **Primary hyperaldosteronism (Conn's syndrome)**:
    - ***Usual adult dose***; Initial dose: 100 mg orally once a day. This dosage may be divided into two daily doses, and increased as tolerated every two to three days to a maximum recommended total daily dose of 400 mg.
  - **Edema** for patients with: **Congestive heart failure (CHF)**, **Cirrhosis** or **Nephrotic syndrome**:
    - ***Usual adult dose for CHF***; 25 mg/day orally.
  - **Essential hypertension**; may be used alone *or* in combination with thiazide or loop diuretics, ***due to***;
    - Synergistic diuretic effect.
    - Correct hypokalemia.

Spironolactone 25 or 50 mg + **HCTZ** 25 or 50 mg (Aldactazide®)
Spironolactone 50 or 100 mg + **Furosemide** 20 or 50 mg (Lasilactone®)

  - ***Usual adult dose for HTN***; 25 to 200 mg/day orally in 1 or 2 divided doses.
  - **Hypokalemia:** ***Usual adult dose***; 25 to 200 mg/day orally in 1 or 2 divided doses.
  - **Antiandrogen**; Hirsutism, acne (in women) & androgenic alopecia.
    - ***Usual adult dose for Hirsutism***; 50 to 200 mg/day orally in 1 or 2 divided doses.
- **Eplerenone** ***uses***;
  - **Congestive heart failure post-myocardial infarction:**
    - ***Usual adult dose;*** Initial dose 25 mg once daily and titrated to the recommended dose of 50 mg once daily, preferably within 4 weeks as tolerated by the patient.
  - **Hypertension:** ***Usual adult dose***; 50 mg once daily.

Side Effects

- **Hyperkalemia**; *due to* reduce urinary excretion of K^+, may cause life-threatening hyperkalemia (cause cardiac irregularities).
  - The **risk of this complication** is ***greatly increased by***;
    - Renal disease.
    - K^+ supplements and diet rich in K^+.
    - β-blockers, NSAIDs, ACEIs, ARBs and Aliskiren.
- **Metabolic acidosis**; *due to* inhibiting H^+ secretion.
- **Endocrine abnormalities**; **Gynecomastia**, **Impotence**, and **benign prostatic hyperplasia** (BPH is very rare) all have been reported only with **Spironolactone**.

Contra indication

- ***Patients with***;
  - Anuria and renal insufficiency.
  - Hyperkalemia.

Drug Interactions

- Concomitant administration of **Spironolactone** *or* **Eplerenone** *with*;
  - **Other K^+-sparing diuretics**.
  - **β-blockers**, **NSAIDs**, **ACEIs**, **ARBs** and **Aliskiren**.
  - **K^+ supplements** and **diet rich in K^+**.
- **Eplerenone** contraindicated with **liver microsomal enzyme inhibitors** (e.g. erythromycin, fluconazole), can increase blood levels of Eplerenone.

- **Diuretics** are ***not*** **part** of the ***standard*** **treatment** for **gestational hypertension** and **edema**. *Their application* is ***limited*** to **special indications**.
- **Hydrochlorothiazide** is the ***drug of choice*** (Category B).
- **Furosemide** *may be* **used** to ***manage*** **heart/kidney failure** (Category C).
- **Spironolactone** *may be* **used** (category C), it may showed ***feminization*** of **male fetuses** or **endocrine** ***dysfunction*** in *both* **male** and **female**.

Non-aldosterone Antagonists (Epithelial Sodium Channel Blockers)

Amiloride (Midamor®) | Triamterene (Dyrenium®)

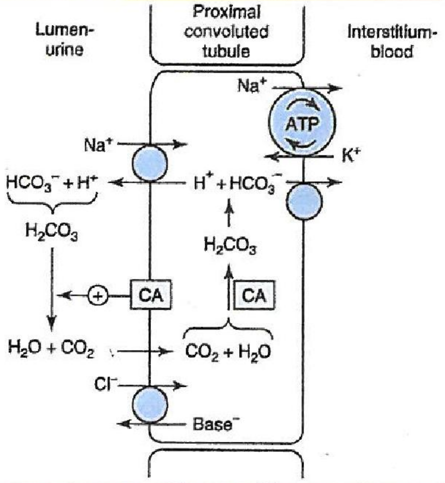
- **Amiloride** [a-MIL-oh-ride] and **Triamterene** [try-AM-the-reen] are direct inhibitors of Na^+ influx in the CCT (cortical collecting tubule).
- ***Mechanism of action***; ***Direct block*** **epithelial sodium channel** (**ENaC**) ⇨ ↓ sodium reabsorption in the **late distal convoluted tubules** and **cortical collecting tubule** in the nephrons ⇨ ↑ loss of Na^+ and water *with* ↓ K^+ and H^+ secretion.
- ***Used*** as **adjunctive treatment** with **thiazide diuretics** or **loop diuretics** in **congestive heart failure** or **hypertension** to;
  - Synergistic diuretic effect.
  - Correct hypokalemia.

Amiloride 5 mg + **Hydrochlorothiazide** 50 mg (Moduretic®)
Triamterene 37.5 mg + **Hydrochlorothiazide** 25 mg (Dyazide®)

- ***Side effects***;
  - Hyperkalemia and metabolic acidosis.
  - **Triamterene** may cause kidney stones (due to slightly soluble in the urine).
- ***Contraindications***; Patients with renal insufficiency and hyperkalemia.
- ***Drug interactions***;
  - ***Concomitant administration with***;
    - **Other K^+-sparing diuretics**.
    - **β-blockers**, **NSAIDs**, **ACEIs**, **ARBs** and **Aliskiren**.
    - **K^+ supplements** and **diet rich in K^+**.
  - **Triamterene** *with* **Indomethacin** has been reported to cause acute renal failure.

Carbonic Anhydrase Inhibitors

- Carbonic anhydrase (CA) enzyme is present in many nephron sites, but the predominant location of this enzyme is the epithelial cells of proximal convoluted tubule (PCT).
- It catalyzes the dehydration of H_2CO_3 to CO_2 at the luminal membrane and rehydration of CO_2 to H_2CO_3 in the PCT as in figure.
- By blocking carbonic anhydrase ⇨ ↓ $NaHCO_3$ reabsorption (block Na/H^+ exchange) and cause diuresis.
- Carbonic anhydrase inhibitors are ***now*** **rarely used as diuretics**.
- ***Pharmacodynamics***;
  - **Kidney**; weak self-limiting diuretic.
  - **Eye**; ↓ synthesis of aqueous humour (↓ IOP).
  - **CNS**; antiepileptic effects & ↑ ventilation.



Acetazolamide (Diamox®) | Methazolamide (Neptazane®)

Dichlorphenamide (Daranide®) | Dorzolamide (Trusopt®) | Brinzolamide (Azopt®)

- **Acetazolamide** [a-set-a-ZOLE-a-mide], **Methazolamide** [meth-a-ZOLE-a-mide], **Dichlorphenamide** [dye-klor-FEN-a-mide], **Dorzolamide** [dor-ZOEL-a-mide] and **Brinzolamide** [brin-ZOE-lah-mide] are sulfonamide derivatives. The prototypical CA inhibitors is **Acetazolamide**.
- ***Uses***;
  - **Diuretics** (***but*** **rarely used as diuretics**).
  - **Glaucoma**; **Acetazolamide** ***dose*** in **open angle** (**orally** or **IV**: 250 mg 1 to 4 times a day) and **close angle** (250 to 500 mg **IV**, may repeat in 2 to 4 hours to a maximum of 1 gram/day).
    Methazolamide ***dose*** in open and closed; 50 to 100 mg orally 2 to 3 times daily.
    Dichlorphenamide ***dose***; ***initial***; 100mg 2 times daily, ***maintenance***; 25-50mg 1 to 3 times daily.
    Dorzolamide (2%) & **Brinzolamide** (1%) ***dose***; 1 drop 3 times daily.
  - **Urinary alkalinization and metabolic alkalosis.**
  - **Acute mountain sickness** (**Altitude sickness**); due to ↑ ventilation.
  - **Adjuvants in the treatment of epilepsy**.
- ***Side effects***;
  - **Hyperchloremic metabolic acidosis**, **hypokalemia** and **hypersensitivity**.
  - **Phosphaturia** and **hypercalciuria**; *due to* alkalinization of urine.
  - *CNS*; **drowsiness** and **paresthesia**.

- **Changes in urinary electrolyte patterns and body pH in response to diuretics;-**

	Urinary electrolytes			
Group	**NaCl**	**$NaHCO_3$**	**K^+**	**Body pH**
Carbonic anhydrase inhibitors	+	+++	+	↓
Loop agents	++++	0	+	↑
Thiazides	++	+	+	↑
Loop agents plus Thiazides	+++++	+	++	↑
K^+-sparing agents	+	(+)	-	↓

+, increase; -, decrease; 0, no change; ↓, acidosis; ↑, alkalosis

(Table from Basic and Clinical Pharmacology, Katzung-Lange, 2012, p257)

Osmotic Diuretics

- **Osmotic diuresis**; is increased urination due to the presence of certain substances in the fluid filtered by the kidneys. This fluid eventually becomes urine. These substances cause additional water to come into the urine, increasing its amount.
- Osmotic diuresis can be caused by high blood sugar (glucose) or by use of certain medications, such as mannitol.

Mannitol (Osmitrol®)

- **Mannitol** [MAN-ih-tole] is classified as a **sugar alcohol**, which is derived from a sugar (mannose) by reduction. Other sugar alcohols include **xylitol** and **sorbitol**. Mannitol and sorbitol are isomers.
- ***Pharmacokinetics***;
  - Mannitol is poorly absorbed by the GIT, when administered orally, it cause osmotic diarrhea rather than diuresis.
  - For systemic effect, mannitol must be given IV.
  - It is not metabolized and it is excreted by glomerular filtration within 30-60 min
- ***Uses***; Mannitol is used clinically in **osmotherapy**;
  - ***Prevention*** and/or ***treatment*** of the **oliguric phase of acute renal failure**.
  - ***Reduction*** of **intracranial pressure (ICP)** and ***treatment*** of **cerebral edema**.
  - ***Reduction*** of elevated **intraocular pressure (IOP)**; when cannot be lowered by other means.
  - ***Promotion*** of **urinary excretion of toxins**.

2) β-Adrenoceptor Blocking Agents

- **All β-blockers** are useful for lowering blood pressure in **mild to moderate hypertension. In severe hypertension**, β-blockers are especially useful in ***preventing*** the **reflex tachycardia** that often results from ***treatment with*** **direct vasodilators.**
- **β-blockers** have been shown to ***reduce*** **mortality after a myocardial infarction** and some also ***reduce*** **mortality in patients with heart failure.**
- ***Mechanism of action***;
  - They are block β-adrenoceptor in the heart ⇨ ***decrease*** **cardiac output** ⇨ ***decrease*** **BP.**
  - **Propranolol** inhibits renin release, and **some of β-blockers** may ↓ peripheral vascular resistance.
- ***β-blockers precautions***;
  - **The β-blockers must be tapered off gradually**; Long-term treatment with a β-blocker ⇨ up-regulation of the β-receptors. ***Sudden stop*** of β-blocker therapy ⇨ increased receptors sensitivity and can worsen angina or hypertension.
  - ***Non-selective β-blockers used with caution*** in **insulin-dependent diabetic patients** (Mask hypoglycemia symptoms).
  - ***Non-selective β-blockers***, are ***contraindicated*** in patients with **COPD** or **asthma.**
  - **β-blocker** ***not used*** with **non-dihydropyridines Ca^{2+} channel blockers** (**Verapamil** and **Diltiazem**) ***to avoid*** **heart block.**
  - **Carvedilol** > **Metoprolol Succinate** > **Bisoprolol** are ***only*** **β-blockers** ***may be used*** in **CHF.**
- ***See*** ANS ***Chapter***; page no 79; for more information.

Propranolol (Inderal®) | **Nadolol** (Corgard®)

- **Propranolol** [proe-PRAN-oh-lole] and **Nadolol** [NAH-doh-lole] are a **non-selective β-blocker drugs**, **Nadolol** is ***more potent*** than **propranolol. Nadolol** has a ***very long*** **duration of action** with ***low*** **lipid solubility** than **propranolol.**
- ***Doses***; - **Propranolol**: (orally) ***initial***; 80 mg/day. ***Maintenance***; 120-240 mg/day (↑ if needed).
  - **Nadolol**: (orally) ***initial dose***; 40 mg/day. ***Maintenance dose***; 40-80 mg/day (↑ if needed).

Metoprolol (Lopressor®) | **Atenolol** (Tenormin®) | **Esmolol** (Brevibloc®)
Bisoprolol (Concor®) | **Nebivolol** (Nebilet®)

- **Metoprolol** [me-TOE-proe-lole], **Atenolol** [a-TEN-oh-lole], **Esmolol** [EZ-moe-lole], **Bisoprolol** [BIS-oh-PROE-lol] and **Nebivolol** [ne-BIV-oh-lol] are ***selective β_1-blockers*** (***cardioselective***).
- Cardioselective drugs may be advantageous in treating hypertensive patients who also suffer from asthma, diabetes, or peripheral vascular disease.
- **Carvedilol**, **Metoprolol** and **Bisoprolol** are ***only β-blockers*** may be used in congestive heart failure.
- **Nebivolol** induce releases of **nitric oxide** (endothelium-derived relaxing factor; EDRF) from endothelial cells and causes ***vasodilation***.
- **Esmolol** is an ***ultra-short-acting***, **half-life** (about 10 minutes). It is only available ***intravenously*** and it is ***used*** during surgery or diagnostic procedures, sometimes for emergency care.
- ***Doses***; - **Metoprolol**: (orally) ***initial dose***; 100 mg/day. ***Maintenance dose***; 100-450 mg/day.
  - **Atenolol**: (orally) 50 mg once daily, ***may be increased*** to 100 mg once daily.
  - **Esmolol**: (IV) ***initial***; 500 mcg/kg/min over 1 min, ***Maintenance***; 50 mcg/kg/min for 4 min.
  - **Bisoprolol**: (orally) ***initial dose***; 5 mg once daily. ***Maintenance***; 5 to 20 mg once daily.
  - **Nebivolol**: (orally) ***initial dose***; 5 mg once daily. ***Maintenance dose***: > 40 mg once daily.

Acebutolol (Sectral®) | **Pindolol** (Visken®) | **Celiprolol** (Selectol®)
Oxprenolol (Trasicor®) | **Penbutolol** (Levatol®)

- **Acebutolol** [a-se-BYOO-toe-lole], **Pindolol** [PIN-doe-lole], **Celiprolol** [SEE-li-proe-lole], **Oxprenolol** [ox-PREN-oh-lole] and **Penbutolol** [pen-byoo-TOH-lol] are partial agonists, i.e, β-blocker with some **intrinsic sympathomimetic activity (ISA), They lower blood pressure** by ***decreasing*** **vascular resistance** and ***depress*** **cardiac output** or **heart rate** less than other β-blockers, ***this may be particularly beneficial for*** **patients** with **bradyarrhythmias** or **peripheral vascular disease.**

- ***Doses***; - **Acebutolol**: (orally) ***initial***: 400 mg once or 200 mg twice. ***Maintenance***: 400 - 800 mg/day.
  - **Pindolol**: (orally) ***initial dose***: 5 mg twice daily. ***Maintenance dose***: 10 to 60 mg/day.
  - **Celiprolol**: (orally) ***initial dose***: 200 mg once daily. ***Maintenance dose***: 400 mg/day.
  - **Oxprenolol**: (orally) 80-160 mg a day, 2 to 3 doses. ***Maximum daily dose*** is 320 mg.
  - **Penbutolol**: (orally) ***initial***: 20 mg once daily. ***Maintenance dose***: 20 to 40 mg once daily.

Labetalol (Trandate®)	**Carvedilol** (Dilatrend®)

- **Labetalol** [lah-BET-a-lole] and **Carvedilol** [KAR-ve-dil-ole] are a ***non-selective*** **β**-adrenergic blocker and ***selective*** α_1-adrenergic blocker.
- **Labetalol** used in treatment of ***chronic*** or ***acute*** **hypertension of *pheochromocytoma* and *hypertensive crisis*.**
- **Carvedilol** reduces mortality in patients with heart failure (***protective effect***) and is therefore particularly ***useful*** in patients with **both heart failure and hypertension**.
- ***Doses***; - **Labetalol**: (orally) ***initial***: 100 mg twice daily. ***Maintenance***: 200 to 400 mg twice daily.
  (IV) 20-80 mg to treat hypertensive crisis.
  - **Carvedilol**: (orally) ***initial***: 6.25 mg twice daily with food. ***Maintenance***: 6.25-25 mg twice

3) Angiotensin-Converting Enzyme Inhibitors (ACEIs)

Captopril (Capoten®)	**Lisinopril** (Zestril®)	**Enalapril** (Renitec®)
Fosinopril (Monopril®)	**Perindopril** (Coversyl®)	**Ramipril** (Tritace®)
Benazepril (Cibacen®)	**Cilazapril** (Zapritens®)	**Imidapril** (Tanatril®)
Zofenopril (Zofecard®)	**Quinapril** (Accupril®)	**Trandolapril** (Mavik®)

- The **hypotensive activity** of ACE inhibitors, ***due to***;
  - ***Blocks*** the **conversion** of **angiotensin I** to **angiotensin II**.
  - ***Inhibits*** the **degradation** of **bradykinin** (vasodilator peptide, **cause** VD via NO release).
- **Cardiac output** and **heart rate** are ***not significantly*** changed.
- **ACE inhibitors *used* alone** or in **combination**.
- **ACE inhibitors** are ***first-line drugs*** for **hypertensive patients** *with* diabetes, chronic kidney disease, and patients at increased risk of coronary artery disease.
- ***ACEIs precautions***;
  - **Hypotension *may occur* after initial dose.**
  - **Avoid K^+ supplements, diet rich in K^+** and **other drugs that increases K^+ level in the blood** e.g. ARBs, Aliskiren and K^+ sparing diuretics; may cause life-threatening hyperkalemia.
  - **ACEIs may develop dry persistence cough and angioedema**; due to increase levels of bradykinin and substance P, this effect resolves within a few days of discontinuation. Can be treated by (***two studies suggested***);
    - **Iron supplements** (e.g. ferrous sulfate) an inhibitor of NO synthase.
    - **Non-steroidal anti-inflammatory drugs**; NSAIDs (e.g. aspirin 500 mg/day).
  - **ACEIs *are* contraindicated *with* pregnancy**; increase risk of fetal malformation.
- ***See* Autacoids *Chapter***; page no 101; for more information about ACEIs.

4) Angiotensin II Receptor Blockers (ARBs)

Losartan (Cozaar®)	**Valsartan** (Diovan®)	**Candesartan** (Atacand®)
Irbesartan (Aprovel®)	**Eprosartan** (Teveten®)	**Telmisartan** (Micardis®)
Olmesartan (Erastapex®)	**Fimasartan** (Kanarb®)	**Azilsartan** (Edarbi®)

- **ARBs *used* alone** or in **combination**. **ARBs** have a ***similar benefits*** to those of ACE inhibitors in patients with **hypertension**, **heart failure** and **chronic kidney disease**.
- ARBs have a ***similar precautions*** to ACE inhibitors, but less in cough and angioedema.
- ARBs ***more selective blockers*** of **angiotensin effect** than ACE inhibitors.
- ***See* Autacoids *Chapter***; page no 103; for more information about ARBs.

5) Direct Renin Inhibitors

Aliskiren (Tekturna®)

- **Aliskiren** [AL-is-KYE-ren] is the ***first*** and ***only*** drug available in a class of drugs called **direct renin inhibitors** (FDA approval in 2007).
- It is ***act by*** binding to active site of renin ⇨ decreasing plasma renin activity ⇨ inhibiting conversion of angiotensinogen to angiotensin I.
- It is ***used*** in **treatment of hypertension** (alone or in combination with other antihypertensive agents).
- It has **long duration of action**, used ***once daily***.
- ***Adverse effects***: **Diarrhea**, **GI symptoms** and **Rash**.
  - Symptoms of hypotension e.g. **headache** and **dizziness** (after initiation treatment).
  - **Angioedema** and **cough**; ***but less common***, than ACE inhibitors or ARBs.
  - May cause **hyperkalemia**.
- ***Contraindication***: **Pregnancy**; it can cause injury and death to the developing.
- ***Drug interactions***: ***with***
  - **ARBs** or **ACEIs** ⇨ ↑ risk of renal impairment, hyperkalemia, and hypotension.
  - **K^+ sparing diuretics** or **K^+ supplements** ⇨ ↑ hyperkalemia.
  - **NSAIDs** ⇨ May reduce the hypotensive effects.
  - **LMEIs** e.g. **Erythromycin** ⇨ ↓ metabolism of Aliskiren ⇨ ↑ it is effect.

6) α-Adrenoceptor Blocking Agents

Prazosin (Minipress®) | Doxazosin (Cardura®) | Terazosin (Hytrin®)

- **Prazosin** [PRAY-zoe-sin], **Doxazosin** [dox-AY-zoe-sin] and **Terazosin** [ter-AY-zoe-sin] are selective competitive α_1 receptors blockers.
- Acts by blocking postsynaptic α_1-adrenoceptors on vascular smooth muscle ⇨ vasodilatation ⇨ ***decrease*** **total peripheral resistance** ⇨ ***decrease*** **blood pressure**.
- The drugs are ***more effective*** **when used in combination** with other agents, such as a β-blockers and a diuretic, than when used alone.
- These drugs are ***used*** **primarily** ***in men with*** **concurrent hypertension and benign prostatic hyperplasia (BPH)**.
- ***Doses***;
  - **Prazosin**: (orally) ***initial***: 1 mg 2-3 times daily. ***Maintenance***: 6-15 mg/d in divided doses.
  - **Doxazosin**: (orally) ***initial***: 1 mg once daily. ***Maintenance***: 1-16 mg once daily.
  - **Terazosin**: (orally) ***initial***: 1 mg once daily at bedtime. ***Maintenance***: 1 to 5 mg once daily.
- ***Most common side effects*** is **first-dose orthostatic hypotension** (***initial syncope attack or first-dose phenomenon***) this include headache, dizziness and palpitations ⇨ to overcome; the first dose must be minimized and giving at bed time.

Phenoxybenzamine (Dibenzyline®) | Phentolamine (Rogitine®)

Tolazoline (Priscoline®)

- **Phenoxybenzamine** [fen-OX-ee-BEN-za-meen], **Phentolamine** [fen-TOL-a-meen] and **Tolazoline** [tol-A-zoe-lin] are non-selective α-adrenoceptor blockers.
- The drugs are **useful in diagnosis** and **treatment** of ***pheochromocytoma***.
- ***See* ANS *Chapter***; page no 73; for more information about α-adrenoceptor blocking agents.

The Spanish researchers found that taking blood pressure medications (ACE inhibitors, ARBs and beta blockers) at bedtime rather than waiting until morning may cut the risk of developing type 2 diabetes by more than half.

7) Calcium Channel Blockers (CCBs)

- There are at least five different types of calcium channels in Homo sapiens: L-, N-, P/Q-, R- and T-type, with a number of classes of blockers, ***but*** almost all of them preferentially or exclusively ***block*** the **L-type voltage-gated calcium channel**.
- **L-type calcium channels *located on*** the **vascular smooth muscle**, **cardiac myocytes**, and **cardiac nodal tissue** (sinoatrial; SA and atrioventricular; AV nodes).
- These channels are ***responsible for*** **regulating the influx of calcium into muscle cells**, which in turn stimulates smooth muscle contraction and cardiac myocyte contraction.
- ***Therefore***, blocking L-type calcium channels in the heart and in smooth muscle of the coronary and peripheral arteriolar vasculature. This ***cause*** **vasodilation**, -ve inotropic, -ve chronotropic and -ve dromotropic. ***N.B***; CCBs do not dilate veins.
- ***There are three classes of CCBs***;
  1) **Dihydropyridines**; ***mostly***; selective for vascular smooth muscle.
  2) **Phenylalkylamines**; ***mostly***; selective for cardiac muscle.
  3) **Benzothiazepines**; ***intermediate between*** phenylalkylamines and dihydropyridines.
- **CCBs** are ***useful*** in the **treatment** of **hypertensive patients** who also have **asthma**, **diabetes**, and/or **peripheral vascular disease**.
- **All CCBs** are ***useful*** in the **treatment** of **angina**. In addition, **non-dihydropyridines CCBs** are ***used*** in the **treatment** of **atrial fibrillation**.

Dihydropyridines		
Nifedipine (Adalat®)	**Amlodipine** (Norvasc®)	**Felodipine** (Plendil®)
Isradipine (DynaCirc®)	**Lacidipine** (Lacipil®)	**Nicardipine** (Cardene®)
Lercanidipine (Care dipine®)	**Nitrendipine** (Cardif®)	**Nimodipine** (Nimotop®)

- **Nifedipine** [nye-FED-i-peen] (is the prototype), **Amlodipine**, [am-LOE-di-peen], **Felodipine** [fe-LOE-di-peen], **Isradipine** [is-RADi-peen], **Lacidipine** [la-SI-di-peen], **Nicardipine** [nye-KAR-di-peen], **Lercanidipine** [ler-kah-NIH-dih-peen], **Nitrendipine** [NYE-tren-di-peen] and **Nimodipine** [nye-MOE-di-peen]. This CCB class is ***easily identified*** by the suffix **"-dipine"**.
- **All dihydropyridines** have a ***much greater affinity*** for **vascular calcium channels *than* for calcium channels in the heart; Show *little* interaction** with other cardiovascular drugs, such as **Digoxin**.
- ***Pharmacokinetics***;
  - **Most of these agents** have ***short half-lives*** (3 to 8 hours) following an oral dose. **Sustained-release (SR)** preparations are available and permit ***once-daily dosing***. **Amlodipine** has a **very long half-life** and does not require a sustained-release formulation.
- ***Indication and dosage***;

Drug	Indication (most common)	Dosage
Nifedipine	Angina, Hypertension, Raynaud's phenomenon	IV; 3-10 mcg/kg. Orally (*not SR*) 20-40 mg 3 times/d.
Amlodipine	Angina, Hypertension	5-10 mg orally once daily
Felodipine	Hypertension	5-10 mg orally once daily
Isradipine	Hypertension	2.5-10 orally twice daily
Lacidipine	Hypertension	2-6 mg orally once daily
Nitrendipine	Hypertension	20 mg orally once or twice daily
Lercanidipine	Angina, Hypertension	20-30 mg once daily at least 15 min before meals
Nicardipine	Angina, Hypertension, Cerebral vasospasm	20-40 mg orally 3 times daily
Nimodipine	Cerebral vasospasm, Subarachnoid Hemorrhage	60 mg orally every 4 hours

- **Nifedipine** may be used for migraine prophylaxis or for premature labor.
- **Felodipine** interact with **grapefruit juice** (grapefruit contains compounds known as furanocoumarins that block the CYP3A4 enzymes).
- **Nimodipine** and **Nicardipine** can ***pass*** **BBB** and is used to prevent cerebral vasospasm.
- **Clevidipine** [kle-VID-a-peen] (Cleviprex®) is a newer agent that is ***formulated*** for **IV use only**.

Phenylalkylamines

Verapamil (Isoptin®)

- **Verapamil** [ver-AP-a-mil] a calcium channel blocker that is a class IV anti-arrhythmia agent.
- It is the only member of this class that is available and the ***least selective*** of any CCBs.
- It has significant effects on ***both*** **cardiac** and **vascular smooth muscle**.
- It is the ***least effective*** of any CCBs on **vascular smooth muscle**.
- It is ***used*** to ***treat*** **hypertension**, **angina** and **supraventricular tachyarrhythmias** and to **prevent migraine** and **cluster headaches**.
- *Adult dose*; Orally (Not SR) 80-160 mg orally 3 times daily. IV 75-150mcg/kg as bolus over at > 2 min.
- *Recent animal studies*;
  - **Verapamil** also inhibits thioredoxin-interacting protein, the protein that leads to the death of pancreatic beta cells that produce insulin, and thus causes diabetes.
  - Data accumulated indicates a verapamil-induced inhibition of the ability of resistant cells to actively extrude chemotherapeutic agents.

Benzothiazepines

Diltiazem (Altiazem®)

- **Diltiazem** [dil-TYE-a-zem] affects ***both*** **cardiac** and **vascular smooth muscle**, ***but*** it has a ***less pronounced*** -ve inotropic effect on the heart compared to that of **verapamil**.
- It is ***used*** in the **treatment** of **hypertension**, **angina**, and **supraventricular tachyarrhythmias**.
- Topical diltiazem as a 2% cream or ointment effective in **treatment chronic anal fissure**, it ***cause*** **muscle relaxation** and ***improve*** **blood flow** to ***facilitate*** **healing**.
- *Adult dose*; Orally (Not SR) 30-80 mg orally 4 times daily. IV 75-150mcg/kg as bolus over at > 2 min.

Side Effects

- **First-degree atrioventricular block** and **constipation** are common dose-dependent side effects of **Verapamil**.
- **Verapamil** and **Diltiazem** ***should be avoided*** in **patients with heart failure** or **with atrioventricular block** due to their -ve inotropic and -ve dromotropic effects.
- **Dizziness**, **headache**, and a **feeling of fatigue** caused by a decrease in blood pressure are more frequent with **dihydropyridines**.
- **Peripheral edema** is commonly reported with **dihydropyridines**.
- **Nifedipine** & **other dihydropyridines** may cause **gingival hyperplasia**.

- ***Generally***; **CCBs are commonly used during pregnancy and lactation** to **treat hypertension**, **arrhythmia**, and **preeclampsia**.
- They have also been ***used*** as **tocolytic agents** to **prevent premature labour** and its complications.
- CCBs is ***only recommended*** **for use during pregnancy *when* benefit outweighs risk.**

8) Centrally Acting Sympathetic Inhibitors

Clonidine (Catapres®)

- **Clonidine** [KLOE-ni-deen] is an α_2 agonist (centrally and peripherally) that is ***used*** for the ***treatment of*** **hypertension** (*other uses see* ANS chapter, page no 63)
- ***It decreases blood pressure by***;
  - **1) Stimulate presynaptic α_2 receptors:**
    - ↓ Presynaptic Ca^{2+} ⇨ ↓ NE release ⇨ ↓ **blood pressure**.
  - **2) Stimulate central α_2 receptors:**
    - ↓ Sympathetic vasomotor centers ⇨ ↓ Sympathetic outflow ⇨ ↓ NE release ⇨ ↓ renin release ⇨ ↓ **blood pressure**.
  - **3) Stimulate I_1 (Imidazoline) receptor:**
    - Sympatho-inhibitory action ⇨ ↓ **blood pressure**.
- ***Adult dose***;
  - **Oral preparation** (Catapres®) ⇨ ***Must be given*** twice a day.
    - ***Initial dose***; 0.1 mg tablet twice daily (morning and bedtime).
    - ***Maintenance dose***; 0.2-0.6 mg per day given in divided doses.
  - **Transdermal preparation** (Catapres-TTS®) ⇨ given once every 7 days.
- The ***most frequent*** adverse effects (dose-related) are:
  - Dry mouth, drowsiness, dizziness, constipation and sedation.
- ***Clonidine therapy should be gradually tapered off***;
  - Clonidine suppresses sympathetic outflow resulting in lower blood pressure, but sudden discontinuation can cause rebound **hypertension (life-threating hypertensive crisis)** due to a rebound in sympathetic outflow. (Treated by α_1 and β blockers).

α-Methyldopa (Aldomet®)

- **Methyldopa** [meth-ill-DOE-puh] is an α_2 agonist that has both central and peripheral effects.

Methyldopa has a dual mechanism of action

1) Methyldopa is converted into the **false transmitter** (metabolite) called; ***alpha-methylnorepinephrine***, in the CNS by dopamine beta-hydroxylase (DBH) enzyme ⇨ The false transmitter is central α_2-agonist ⇨ ↓ sympathetic outflow ⇨ ↓ NE release ⇨ ↓ renin release ⇨ ↓ blood pressure.
2) It is a **competitive inhibitor of dopa-decarboxylase** enzyme ⇨ which converts L-dopa into dopamine. Dopamine is a precursor for norepinephrine and subsequently epinephrine.

- It is ***mainly used*** for ***management of*** **hypertension in pregnancy** (FDA pregnancy category B).
- ***Used with caution*** in **lactating women** (appears in breast milk).
- ***Adult dose***;
  - ***Initial dose***; 250 mg orally 2-3 times a day in the first 48 hours.
  - ***Maintenance dose***; 500 mg to 2 g orally divided in 2 to 4 doses, up to a maximum of 3 g/day.
  - ***Hypertensive emergency***; 250 to 500 mg IV over 30 to 60 minutes every 6 hours up to a maximum of 1 g every 6 hours or 4 g/day.

Selective Imidazoline Receptors Agonists

Rilmenidine (Hyperium®)	Moxonidine (Cynt®)

- ***Used*** in ***mild to moderate*** **essential hypertension**.
- **Moxonidine** may also promote sodium excretion, improve insulin resistance and glucose tolerance & protect against hypertensive target organ damage, such as kidney disease and cardiac hypertrophy.

9) Peripherally Acting Sympathetic Inhibitors

Guanethidine (Ismelin®)

- **Guanethidine** [gwha-NETH-ih-deen] is an **antihypertensive drug** that reduces the release of catecholamines, such as norepinephrine.
- It acts by ***blocking the release*** of stored **norepinephrine** (NE) (replacing NE in these vesicles) ⇨ ***gradual*** depletion of NE stores in the nerve endings ⇨ ***gradual*** decrease in BP and HR.
- It is ***used*** in the treatment of ***moderate*** and ***severe*** **hypertension** and **renal hypertension**.
- *Side effects*: **Bradycardia, orthostatic hypotension, failure of ejaculation** and **nasal congestion**.

Reserpine (Hypoten®)

- **Reserpine** [re-SER-peen] is a **plant alkaloid** from dried root of ***Rauwolfia serpentina***.
- It acts by irreversibly blocks vesicular monoamine transporter (VMAT) (block Mg^{2+}/adenosine triphosphate-dependent transport) of monoamine neurotransmitters (norepinephrine, dopamine, and serotonin) from storage vesicles in the adrenergic nerve terminals in all body tissues.
- It has a ***slow onset***, a ***long duration*** of action.
- ***After discontinuation*** ⇨ The effects persist for **many days**.
- It is ***used*** in the treatment of ***mild*** **hypertension**.
- ***Most common side effects***: diarrhea, hyperacidity, bradycardia and nasal congestion.

10) Ganglionic Blockers (GBs)

Trimethaphan (Arfonad®)	**Mecamylamine** (Inversine®)
- **Trimethaphan** [trye-METH-a-fan].	- **Mecamylamine** [meck-a-MILL-a-meen].
- Mono sulfonium (S^+).	- Secondary amine.
- Don't pass BBB.	- Pass BBB.
- Ultra short duration of action (10 to 15 min.).	- Longer duration of action.
- Not given orally (IV).	- Given orally.
- Treatment emergency hypertension.	- Treatment moderate hypertension.
- Cause histamine release ⇨ Flushing.	- Not cause histamine release.

11) Vasodilators

- Vasodilators, are drugs or substances that cause vasodilation.
- ***Classification of vasodilators drugs according to mechanism of action***;

1) Release of NO from drug or endothelium;

- **Sodium nitroprusside** and **Nitrates**.

2) Reduction of Ca^{2+} influx;

- **Verapamil**, **Diltiazem** and **Nifedipine** (and other dihydropyridines).

3) Hyperpolarization of smooth muscle membrane through opening K^+ channels;

- **Hydralazine**, **Minoxidil** and **Diazoxide**.

4) Activation of dopamine receptors;

- **Fenoldopam**.

- All the vasodilators that are useful in hypertension by relax smooth muscle of arterioles.
- Sodium nitroprusside and the nitrates also relax veins.
- Nitrates are used mainly in angina (seen later; page no. 149).

Hydralazine (Apresoline®)

- **Hydralazine** [hye-DRAL-a-zeen] is a ***direct vasodilator***, it **dilates arterioles *but* not veins.**

Mechanism OF Action

- **The exact mechanism of action** is ***not fully understood***;
  - Hydralazine altering cellular calcium metabolism, i.e. hydralazine causes smooth muscle hyperpolarization quite likely through the opening of K^+-channels. It also may inhibit IP_3-induced release of calcium from the smooth muscle sarcoplasmic reticulum.
- It also ↑ plasma renin concentration ⇨ sodium and water retention.

Therapeutic Uses

- *Uses*;
  - In **Severe essential hypertension *when*** the drug cannot be given orally or when there is an urgent need to lower blood pressure.
  - ***Commonly* used in combination *with* nitrates** for the **treatment of CHF in self-identified African American populations**.
  - **Oral hydralazine** is effective as **monotherapy *or*** as **add-on therapy** to **methyldopa** in the long term **management of chronic hypertension in pregnancy**.
- *Adult dose*;
  - ***Oral dose***: 10 mg orally 4 times a day for the first 2 to 4 days. ***Increase*** to 25 mg orally 4 times a day for the balance of the first week. ***For the second and subsequent weeks***, increase dosage to 50 mg orally 4 times a day.
  - ***Hypertensive emergency***; Usual dose: 20 to 40 mg IV or IM, repeated as necessary (patients with marked renal damage may require a lower dose).

Side Effects

- ***Most common***; **Headache, nausea, anorexia, palpitation, sweating** and **flushing.**
- Up to 20% of patients (how slowly acetylate the drug) who receive 400 mg/day or more mainly develop a **systemic lupus erythematosus syndrome.**

Minoxidil (Loniten®)

- **Minoxidil** [min-OX-i-dill] is a ***very efficacious* orally active vasodilator.**
- Like **hydralazine, minoxidil dilates arterioles *but* not veins.**
- ***Because*** of its **greater potential antihypertensive effect, minoxidil *should replace* hydralazine *when* maximal dose of the hydralazine is not effective.**
- **Minoxidil** and **hydralazine** is almost always (***should be***) ***administered in combination*** with a **β-blockers** (to balance the reflex tachycardia) and a **loop diuretics** (to decrease sodium retention).
- *Uses*;
  - **Oral minoxidil**; **Treatment of severe hypertension**.
    - *Adult dose*; 5 mg as a single daily dose, may be increased to 10, 20 and then to 40 mg. The effective dosage range is usually 10 to 40 mg per day. The maximum recommended dosage is 100 mg/day.
  - **Topical minoxidil** (Rogaine®); used in topical treatment (regrowth) of **androgenic alopecia** in males and females and **stabilisation of hair loss** in patients with androgenic alopecia (*See* dermatology chapter).
- ***Vasodilator* mechanism of action**; Minoxidil is a potassium channel opener, act by opening K^+-channels in smooth muscle membrane which closes voltage-gated calcium channels and decreases intracellular calcium.
- ***Most common side effects;*** **Tachycardia**, **angina** and **edema** are observed when doses of β-blockers and diuretics are inadequate.
  - **Headache**, **sweating** and **hypertrichosis**.

Sodium Nitroprusside (Nipride®)

- **Sodium Nitroprusside** [SOE-dee-um nye-troe-PRUS-ide], is a ***powerful*** **short acting parenterally vasodilator** that is ***used*** in treating **hypertensive emergencies** as well as **sever heart failure**.
- It is **dilates *both* arterial** and **venous vessels**.
- ***Pharmacokinetics***;
  - Chemically, is an inorganic compound with the formula $Na_2[Fe(CN)_5NO]$, It is rapidly metabolized by uptake into red blood cells, with liberation of cyanide. Cyanide in turn is metabolized by the mitochondrial enzyme in the presence of sulfur donor to the less toxic thiocyanate. Thiocyanate is slowly eliminated by the kidney.
  - *Duration of action*; 1 - 10 minutes after infusion is stopped.
  - ***Dose***; 0.5 mcg/kg/min, maximum dose; 10 mcg/kg/min.
- ***Mechanism of action***; Sodium nitroprusside breaks down in circulation to release nitric oxide (NO), NO activates guanylate cyclase in vascular smooth muscle and increases intracellular production of cGMP, the end result is vascular smooth muscle relaxation.
- ***Toxicity***; The most serious toxicity is related to accumulation of cyanide and may cause death. Administration of **sodium thiosulfate** (sulfur donor) facilitates cyanide metabolism. **Hydroxocobalamin (vit. B_{12})** combined with cyanide to form the non-toxic cyanocobalamin.

Diazoxide (Proglycem®)

- **Diazoxide** [dye-az-OX-ide] is a (non-diuretic thiazide) long acting **arteriolar dilator** that is ***used*** to **treat hypertensive emergencies**.
- It is a ***potassium channel activator***, which causes vascular smooth muscle relaxation.
- It is also **inhibits the secretion of insulin** from the pancreas, thus it is ***used*** to **counter hypoglycemia** in disease states such as insulinoma (a tumor producing insulin) or congenital hyperinsulinism.
- ***FDA warning*** (7/2015) pulmonary hypertension has been reported in infants and newborns treated with diazoxide.

Fenoldopam (Corlopam®)

- **Fenoldopam** [fen-OL-de-pam] is an agonist of peripheral dopamine D_1 receptors.
- It is a racemic mixture and the R-isomer is the active component.
- ***Routes of administration***: for **continuous IV infusion** only ⇨ due to extensive first-pass metabolism and short half-life elimination (10 minutes).
- ***Period of administration***: up to 48 hours in adults - up to 4 hours in pediatric.
- ***Mechanism of action***: **rapid-acting vasodilator** ⇨ agonist of peripheral dopamine D_1 receptors ⇨ VD of renal blood vessels ⇨ diuresis.
- ***Uses***: treat **severe hypertension** in hospitalized patients.
- ***Dose***: initial; 0.1 mcg/kg/min, the dose is titrated upward every 15 or 20 min. to a maximum dose 1.6 mcg/kg/min.
- ***Adverse effects***: Headache, flushing, dizziness, nausea and tachycardia (due to vasodilation).

12) Natural Antihypertensive Agents

- ***The following agents were identified***: coenzyme Q10 (CoQ10), ubiquinone, garlic, arginine, fish oil, hawthorn, olive oil, vitamin C, vitamin E, skullcap, barberry, betel nut, bishop's weed, bitter melon, cat's claw, celery, Eleutherococcus, gotu kola, guar gum, herbal diuretics, hibiscus, holly, jiaogulan, procaine, lemongrass, mistletoe, morinda, *Nigella sativa*, oil of evening primrose, passion flower, periwinkle, reishi mushroom, rhubarb, saffron, stevia, veratrum, white hellebore, willard water, withania, yellow root, yohimbine, and yucca.
- The degree of antihypertensive efficacy is rarely impressive when compared with the blood pressure reduction that can be documented with the incorporation of lifestyle modifications (*include* DASH).

Hibiscus Tea (*Hibiscus sabdariffa*)

- **Hibiscus tea** is a herbal tea made as an infusion from crimson or deep magenta-coloured calyces (sepals) of the roselle (*Hibiscus sabdariffa*) flower (in Egypt called Karkade).
- Studies has shown that drinking hibiscus tea may lower blood pressure in people with type 2 diabetes, prehypertension or mild hypertension. However, there is ***no reliable evidence*** to support recommending hibiscus tea in the treatment of primary hypertension.
- Drinking 3 cups of hibiscus tea daily for 6 weeks reduced systolic blood pressure by 7 mm Hg in prehypertensive and mildly hypertensive.
- Hibiscus flowers contain **anthocyanins**, which are believed to be the active antihypertensive compounds, acting as ACE inhibitors.
- A study compared the effectiveness of hibiscus to the ACE-inhibiting drug captopril (9.6 mg of total anthocyanins and captopril 50 mg/day); hibiscus worked as well as the drug captopril and not show significant differences relative to hypotensive effect, antihypertensive effectiveness, and tolerability.
- There is **no difference** between drinking hibiscus **cold *or* hot**.

Co-Enzyme Q_{10}

- Coenzyme Q-10 (CoQ-10) is a natural antioxidant (is a vitamin-like substance) synthesized by the body, found in many foods & available as a supplement, found in small amounts in meats & seafood.
- CoQ10 may play a role in treating heart and blood vessel conditions such as CHF, angina and hypertension.
- CoQ10 may play a role in reducing the number and severity of migraine headaches, and improving sperm motility in men.
- There is no official daily value recommendation, but ***suggests*** at least 90 to 120 mg/day of supplemental CoQ10 for any adult with a family history of heart problems, or who is at increased risk for cardiovascular disease.
- Researchers concluded that CoQ10 has the potential to lower systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by 10 mm Hg, without significant side effects.
- Statins (class of lipid lowering drugs) are well-tolerated by most people, they do have side effects, including muscle and joint aches and a rare condition that causes muscle cells to break down. Some researchers have proposed that taking a CoQ10 might reduce the risk of these side effects.
- Some research has indicated therapeutic value in high doses to slow the progression of Parkinson's disease.

➢ Hypertensive Crisis :-

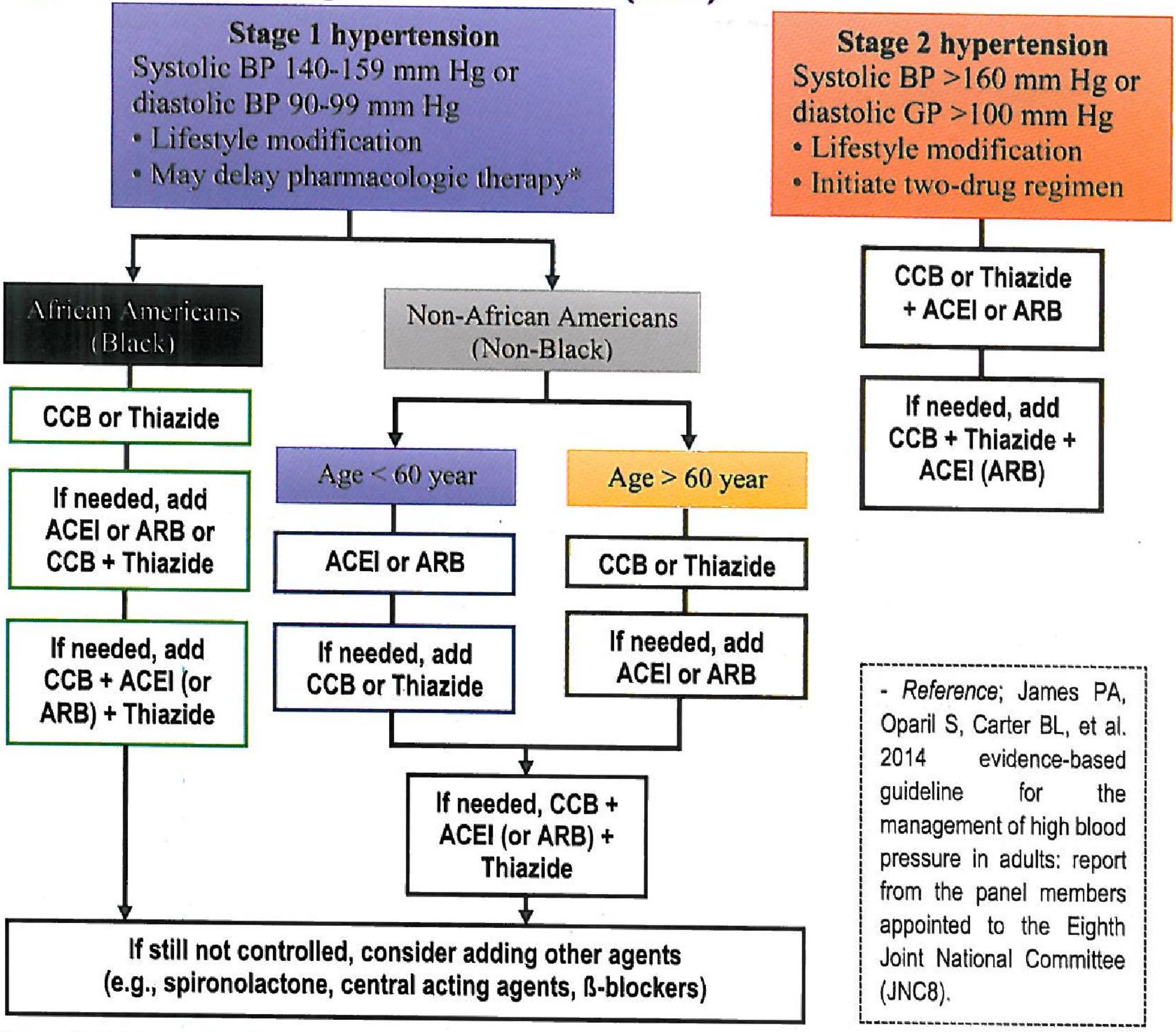
- *Hypertensive crisis*; patients with blood pressures (BP) ≥ 180/110 mm Hg.
  - This condition has been classified as hypertensive emergencies and hypertensive urgencies;
    - **Hypertensive Urgency**;
      - Elevations in BP (≥ 180/110 mm Hg) without progressive target-organ damage.
      - May or may not experience one or more of these symptoms: severe headache, shortness of breath, nosebleeds and severe anxiety.
    - **Hypertensive Emergency**;
      - Severe elevations in BP (≥ 180/110 mm Hg) with the presence of acute or ongoing target-organ damage.
      - Acute target-organ damage can include; hypertensive encephalopathy, intracranial hemorrhage, acute myocardial infarction, acute heart failure, pulmonary edema (shortness of breath), aortic dissection, retinopathy or papilledema, decreased urine output or acute renal failure and eclampsia.
- ***Goals and treatment options***;

Hypertensive Urgency	Hypertensive Emergency
- Managed by using oral antihypertensive agents. - Treatment is initiated with very low doses of oral agents using incremental doses as needed and avoiding large starting doses that may result in excessive blood pressure reduction. - The initial goal is to reduce blood pressure to 160/110 mm Hg over several hours to days. - Mean arterial pressure (MAP) should be reduced by no more than 25% within the first 24 hours. - All patients with hypertensive urgency should be reevaluated within 7 days. - ***Specific agents;*** - **Captopril**; 25 mg oral initially, followed by 50-100 mg time 90-120 minutes later, until the target BP is achieved. - **Nicardipine**; 30 mg oral initially, repeated every 8 hours until the target is achieved. - **Labetalol**; 200 mg orally, repeated every 3-4 hours until the target is achieved - **Clonidine**; 0.1-0.2 mg orally, followed by 0.05-0.1 mg every 1 hour until target is achieved (max. dose of 0.7 mg) - **Nifedipine**; 10-20 mg repeated every 6 to 8 hours until target is achieved.	- Managed by using IV antihypertensive agents. - Patients are usually admitted for intensive care unit (ICU) care and close follow-up. - Reducing the mean arterial pressure (MAP) by no more than 25% or diastolic BP to 100-110 mm Hg within 30-60 minutes. - ***Specific agents (Agents are chosen on the basis of patient characteristics); (See table below)*** - **Sodium Nitroprusside**; 0.25-10 mcg/kg/min., maximum 3 mcg/kg/min. - **Fenoldopam**; 0.1 mcg/kg/min., maximum 1.6 mcg/kg/min. - **Nitroglycerin**; 5-10 mcg/min., maximum 100 mcg/min. - **Enalaprilat**; 0.625-1.25 mg every 4–6 hours, maximum 5 mg every 6 hours. - **Hydralazine**; 5-10 mg every 4-6 hours. - **Nicardipine**; 5-15 mg/hour, max. 15 mg/hour. - **Esmolol**; 250-400-mcg/kg IV Bolus, then a 50-100-mcg/kg/min. infusion, maximum 300 mcg/kg/minute. - **Labetalol**; 20–80 mg IV Bolus every 15 minutes or 0.5–2 mg/min., max 300 mg/24 h. - **Phentolamine**; 5–15 mg IV bolus.

- ***Preferred agents in treatment of specific types of hypertensive emergencies***;

Types of emergency	Preferred agents
Hypertensive encephalopathy	Nitroprusside, Labetalol, Fenoldopam, Nicardipine
Subarachnoid hemorrhage	Nimodipine, Labetalol, Nicardipine
Cerebrovascular accident (CVA)	Labetalol , Nitroprusside, Enalaprilat
Acute renal failure	Fenoldopam, Nicardipine
Acute aortic dissection	Labetalol, Esmolol (β-Blocker; must precede other agents) alone or in combination with Nicardipine, Clevidipine or nitroprusside
Acute pulmonary edema	Nitroglycerin or {Nitroprusside ± ACE inhibitor}
Acute myocardial infarction	Nitroglycerin + β-Blocker
Pheochromocytoma, Cocaine	{Nitroprusside + Labetalol} or Phentolamine
Eclampsia	Methyldopa, Magnesium sulfate (do not use with CCBs), Hydralazine

➢ Hypertension Management Guideline (2014):-



Stage 1 hypertension
Systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg
- Lifestyle modification
- May delay pharmacologic therapy*

African Americans (Black)
- CCB or Thiazide
- If needed, add ACEI or ARB or CCB + Thiazide
- If needed, add CCB + ACEI (or ARB) + Thiazide

Non-African Americans (Non-Black)

Age < 60 year
- ACEI or ARB
- If needed, add CCB or Thiazide

Age > 60 year
- CCB or Thiazide
- If needed, add ACEI or ARB

If needed, CCB + ACEI (or ARB) + Thiazide

If still not controlled, consider adding other agents (e.g., spironolactone, central acting agents, ß-blockers)

Stage 2 hypertension
Systolic BP >160 mm Hg or diastolic GP >100 mm Hg
- Lifestyle modification
- Initiate two-drug regimen

CCB or Thiazide + ACEI or ARB

If needed, add CCB + Thiazide + ACEI (ARB)

- *Reference*; James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC8).

➢ Special Populations:-

- Diuretics
- β-blockers
- ACEIs
- ARBs
- Renin Inhibitors

- α-blockers
- CCBs
- Centrally-acting inhibitors
- Peripherally-acting inhibitors
- Vasodilators

Population or Disease State	Preferred Agents	Avoid Agents
- African Americans and Elderly	Thiazide, CCB	
- Pregnancy	α-Methyldopa, CCB, Labetalol	ACEI, ARB, Aliskiren and ....
- Coronary Diseases (Angina & MI)	β-blocker, CCB, ACEI, ARB	
- Asthma and COPD	CCB	β-blockers, ACEI, ARB
- Benign Prostatic Hyperplasia	α-blocker	
- Depression	CCB, ACEI, ARB	Centrally acting inhibitors, β-blockers, Reserpine
- Diabetes Mellitus	CCB, ACEI, ARB	β-blockers
- Gout	CCB, ACEI, ARB	Diuretics
- Heart Failure	ACEI, ARB, β-blocker	
- Hyperlipidemia	CCB, ACEI, ARB	β-blockers, Diuretics
- Migraine	β-blocker, CCB	
- Osteoporosis	Thiazide	Loop diuretics
- Peripheral Vascular Diseases	α-blockers, Dihydropyridines CCB	β-blockers
- Renal Diseases	Loop diuretics	Thiazide diuretics

Hypertension during Pregnancy

➢ Background:-

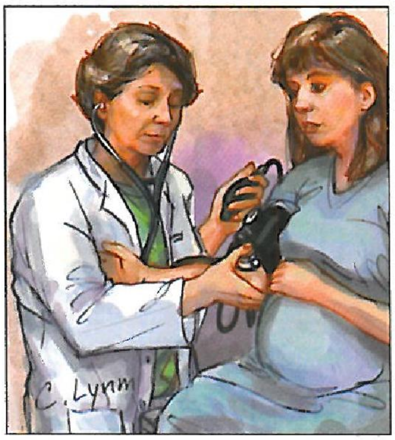
- Hypertension can develop during pregnancy or can be pre-existing.
- Although many pregnant women with high blood pressure have healthy babies without serious problems.
- High blood pressure can be dangerous for both the mother and the fetus.
- Women with pre-existing high blood pressure are more likely to have certain complications during pregnancy that those with normal BP.

➢ What are the effects of hypertension in pregnancy?

- The effects of high blood pressure range from mild to severe.
- High blood pressure can harm the mother's kidneys and other organs, and it can cause low birth weight and early delivery.
- In the most serious cases, the mother develops "**toxemia of pregnancy**" which can threaten the lives of both the mother and the fetus.
- Toxemia of pregnancy is a common name used to describe preeclampsia and eclampsia.
- Hypertensive disorders of pregnancy are one of the most common causes of death due to pregnancy (they resulted in 29,000 deaths in 2013).

➢ Risk factors:-

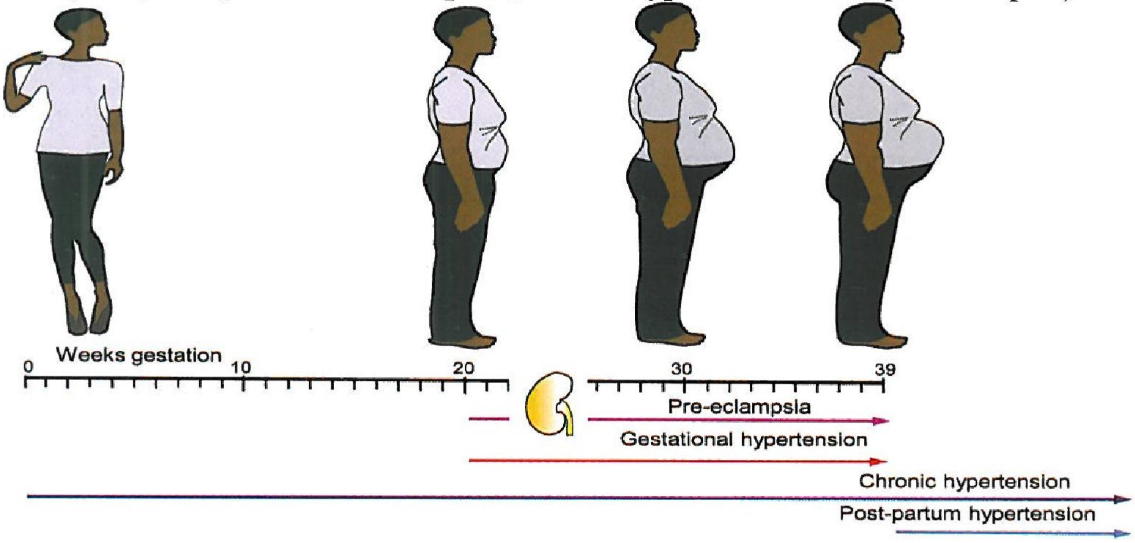
- ***Maternal related factors***:
  - Obesity (BMI ≥30) or age 35 years or more.
  - Past history of hypertension or renal diseases.
  - Adolescent pregnancy or new paternity.
- ***Pregnancy related factors***:
  - Multiple gestation (twins or triplets, etc.).
  - Placental abnormalities.
- ***Family history related factors***:
  - Family history of pre-eclampsia.
  - African American race.



➢ Most common types of hypertension during pregnancy:-

1) **Gestational Hypertension.**
2) **Pre-eclampsia.**
3) **Eclampsia.**
4) **Chronic Hypertension.**
5) **Superimposed Pre-eclampsia (chronic hypertension with preeclampsia).**

Simply;
Mild Hypertension; 140-149/90-99
Moderate Hypertension; 150-159/100-109
Severe Hypertension; 160-more/110-more



1) Gestational Hypertension

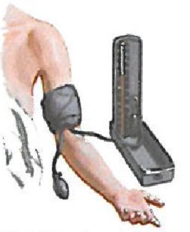
- *Also known as* pregnancy-induced hypertension (PIH).
- *Normal* blood pressure before marriage.
- Develops *after* 20 weeks of pregnancy.
- *BP more than* or *equal* 140/90 mm Hg.
- *No* proteinuria.*
- BP *returns to normal* after 12 weeks of delivery.
- *Some women* with gestational hypertension *eventually develop* preeclampsia.

2) Pre-eclampsia (PE)

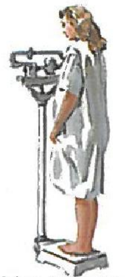
- **Preeclampsia** is a *pregnancy complication* characterized by high blood pressure and signs of damage to another organ system (often the kidneys). It is affects 2-8% of pregnancies worldwide.

➢ **Mild Pre-eclampsia :**

- Develops *after* 20 weeks of pregnancy.
- *BP more than* or *equal* 140/90 mm Hg.
- **Proteinuria** (≥ 300 mg/day).*
- BP *returns to normal* after 12 weeks of delivery.



Mild; BP ≥ 140/90 mm Hg
Severe; BP ≥ 160/110 mm Hg

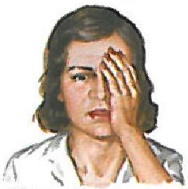


Sudden Weight Gain

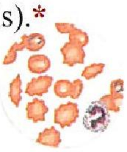
➢ **Severe Pre-eclampsia:**

- Develops *after* 20 weeks of pregnancy.
- *BP more than* or *equal* 160/110 mm Hg.
- **Proteinuria** (≥ 2-5 g/day).*
- **Thrombocytopenia** (<100,000/microliter).*
- **Blurred vision** and **persistent headache.***
- **Sudden weight gain.***
- *Impaired* **kidney function** (oliguria, ↑ creatinine levels).*
- *Impaired* **liver function** (↑ AST and ALT levels).*
- **Swelling** (edema) particularly in face and hands.*
- **Pulmonary edema** (shortness of breath).
- BP *returns to normal* after 12 weeks of delivery.
- Pre-eclampsia, *if untreated* ⇨ result in **seizures** at which point it is known as **eclampsia**.

Puffiness of face



Blurred Vision and Headache



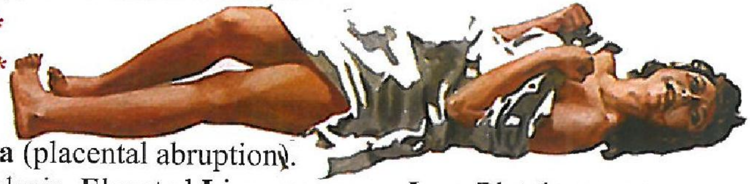
Thrombocytopenia

Pedal edema

Proteinuria

3) Eclampsia

- Eclampsia is a *severe form* of **pre-eclampsia**.
- **Eclampsia** is *considered a* **hypertensive crisis** (*Emergency*).
- **Symptoms** *same as* **severe pre-eclampsia** *in addition to*;
  - **Onset of seizures** (convulsions); tonic-clonic seizures.*
  - **High proteinuria** (> 5 g/day).*
  - **Upper right abdominal pain.***
  - *Possible Complications*;*
    - **Separation of the placenta** (placental abruption).
    - **HELLP syndrome**; **H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelet count.
    - **Premature delivery** that leads to complications in the baby.



4) Chronic Hypertension

- Hypertension was present before pregnancy.*
- Not resolved after labour.*
- Increase risk of developing preeclampsia (Superimposed Pre-eclampsia).

5) Superimposed Pre-eclampsia

- Hypertension was present before pregnancy (Ghronic).*
- Sudden increase in proteinuria and BP with decrease in platelet count.*
- High risk for poor perinatal outcome and placental abruption.

Treatments of Hypertension During Pregnancy

➢ **Pre-pregnancy Advice:-**

- Stop antihypertensive treatment in women taking ACEIs, ARBs, Aliskiren or thiazides there is an increased risk of congenital malformation if these drugs are taken during pregnancy.

➢ **Nutritional Supplements**:-

- Do not recommend the following supplements only with the aim of preventing hypertensive during pregnancy;

- Magnesium, folic acid, antioxidants (vitamins C and E), fish oils and garlic.

➢ **Prevention of Pre-eclampsia:-**

- **Calcium**: ***may be*** **useful** in populations with low calcium intake.
- **Low-dose aspirin** (75 mg/day): from 12 weeks until birth, may have ***slight effect*** to ***reduce*** **preeclampsia** and adverse perinatal outcomes.
- **Bed rest** or **salt restriction**: ***no*** **evidence of benefit.**

➢ **Medications:-**

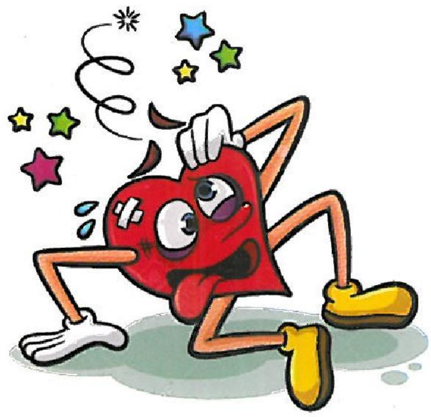
- ***Mild to moderate hypertension***;
  - **Methyldopa** (page no 131); is a drug of choice for control of mild to moderate hypertension in pregnancy, but it is a mild antihypertensive effect with a slow onset of action and associated fatigue.
  - **Labetalol** (page no 127); is more rapid onset of action, may be given orally or parenterally, and is generally preferred as a first-line agent.
  - **Nifedipine** (page no 129); long acting is a reasonable medication to treat chronic hypertension.
  - **Hydralazine** (page no 133); (Oral), is effective as monotherapy or as add-on therapy to methyldopa in the long term management of chronic hypertension in pregnancy.
- ***Severe hypertension***;
  - ***First-line medications***;
    - **Hydralazine** and **labetalol** (**IV**) have long been considered first-line drugs for the management of acute-onset and severe hypertension in pregnancy.
    - Parenteral labetalol should be avoided in women with asthma or CHF.
  - ***Second-line medications***, if the first-line is failed;
    - **Sodium nitroprusside** should be reserved for extreme emergencies and used for the shortest amount of time possible because of concerns about cyanide and thiocyanate toxicity in the mother and fetus or new-born.
- ***Eclampsia seizures***;
  - **Magnesium sulfate** remains the drug of choice for seizure prophylaxis in severe preeclampsia and for controlling seizures in eclampsia.
    - ***Dose***; loading dose of 4 to 6 g given over 15 to 20 minutes, followed by a maintenance dose of 2 g/h as a continuous IV solution.
    - ***Mechanism of action***; Mg^{2+} is a unique Ca^{2+} antagonist as it can act on most types of calcium channels in vascular smooth muscle, may due it cause cerebral vasodilation, thus reducing ischemia generated by cerebral vasospasm during an eclamptic event.

Hypotension

Hypotension (Low Blood Pressure):-

- ***Low blood pressure***; the force of blood pushing by the heart against the walls of the arteries lower than normal.
- ***Hypotension*** is ***generally*** considered as systolic blood pressure less than 90 mm Hg or diastolic less than 60 mm Hg.
- ***Severely*** **hypotension** can deprive the brain and other vital organs of oxygen and nutrients, leading to a life-threatening condition called **shock**.
- ***Causes*** of hypotension can range from dehydration to serious medical or surgical disorders.

Symptoms:-



- Dizziness or lightheadedness.
- Fainting (syncope).
- Lack of concentration.
- Blurred vision.
- Nausea.
- Cold, clammy, pale skin.
- Rapid, shallow breathing.
- Fatigue.
- Depression.
- Thirst.

Causes:-

- **Conditions that can cause low blood pressure**:
  - **Decrease blood volume (*Hypovolemia* or *Dehydration*)**;
    - Hemorrhage (blood loss).
    - Insufficient fluid intake (starvation).
    - Excessive fluid losses (diarrhea or vomiting).
      - **N.B**; ***hypovolemic shock***; is a life-threatening complication of dehydration.
  - **Decrease cardiac output**;
    - Extremely low heart rate, heart failure or heart valve problems.
  - **Excessive vasodilation**;
    - **Severe infection** (***septicemia***); can lead to a life-threatening drop in blood pressure called ***septic shock***.
    - **Severe allergic reaction** (***anaphylaxis***); is a severe and potentially life-threatening allergic reaction.
  - **Endocrine problems**;
    - Adrenal insufficiency (Addison's disease; hyposecretion secretion of adrenocortical hormones)
    - Hypothyroidism and parathyroid disease.
    - Low blood sugar (hypoglycemia).
  - **Pregnancy**;
    - Hypotension during pregnancy may occurs because the circulation expands during pregnancy and hormonal changes cause the blood vessels to dilate, leading to a lowering of blood pressure.
  - **Lack of nutrients in diet**;
    - Lack of the essential vitamins B_{12} and folic acid can cause **anemia**.
  - **Prolonged bed rest**.
- **Medications that can cause low blood pressure**:
  - Diuretics and other antihypertensive drugs, tricyclic antidepressants, erectile dysfunction drugs (such as sildenafil) particularly in combination with nitroglycerin.

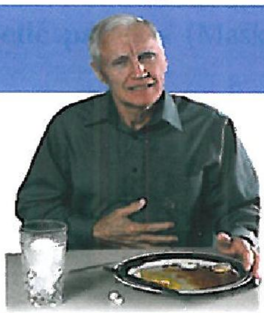
➢ Types of hypotension:-

- **Most common types of hypotension depending on the causes and other factors;**

Orthostatic (Postural) Hypotension
(Low blood pressure on standing up)

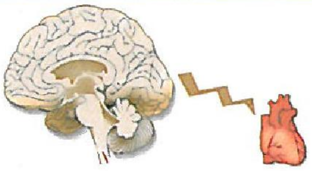
- Sudden drop in blood pressure when stand up from a sitting position or after lying down ⇨ the gravity cause blood to pool in the legs ⇨ the body compensates this by reflex tachycardia and vasoconstriction, ***but*** in people with orthostatic hypotension this compensating mechanism fails and blood pressure falls leading to dizziness, lightheadedness, blurred vision and even fainting.
- Orthostatic hypotension is especially common in older adults, with as many as 20% of those older than age 65, but orthostatic hypotension can also affect young.

Postprandial Hypotension
(Low blood pressure after eating)



- Sudden drop in blood pressure after eating ⇨ due to large amount of blood flows to the digestive tract after eating ⇨ the body compensates this by reflex tachycardia and vasoconstriction, ***but*** in people with postprandial hypotension the autonomic nervous system not compensating appropriately, because of aging or a specific disorder such as Parkinson's disease.
- Postprandial hypotension is especially common in older adults.

Neurally Mediated Hypotension
(Low blood pressure from faulty brain signals)



- Blood pressure drop after standing for long periods, leading to signs and symptoms such as dizziness nausea and fainting.
- It occurs because of a miscommunication between heart and brain.
- Mostly affects young people.
- Stand for extended periods ⇨ blood pools in legs ⇨ nerves in the heart send faulty signals to the brain (that blood pressure is too high) ⇨ As a result, the brain decrease the heart rate ⇨ decreasing blood pressure. This causes more blood to pool in the legs and less blood to reach the brain, leading to lightheadedness and fainting (Neurocardiogenic syncope).
- **Dysautonomia**; is an autonomic nervous system (ANS) malfunctions, is a type of neuropathy affecting the nerves that carry information from the brain and spinal cord to the heart, bladder, intestines, sweat glands, pupils, and blood vessels.

Multiple System Atrophy (MSA) with Orthostatic Hypotension
(Low blood pressure due to nervous system damage)

- Multiple System Atrophy (MSA), also called Shy-Drager syndrome.
- This rare disorder causes progressive damage to the autonomic nervous system.
- ANS controls involuntary functions such as blood pressure, heart rate, breathing and digestion.
- This condition can be associated with muscle tremors, slowed movement, problems with coordination and speech, and incontinence, its main characteristic is severe orthostatic hypotension in combination with very high blood pressure when lying down.

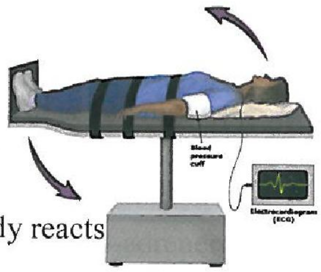
➢ Complications:-

- Moderate forms of low blood pressure can cause not only dizziness and weakness but also fainting and a risk of injury from falls.
- Severely low blood pressure from any cause can deprive the body of enough oxygen to carry out its normal functions, leading to damage of heart and brain.
- Shock and death are the end result of prolonged low blood pressure.

➢ N.B:-

- **Acute hypotension**; often associated with the different forms of shock including: septic (septicaemia), cardiogenic (MI), hypovolaemia (haemorrhage, burns and dehydration), anaphylactic (hypersensitivity reaction), neurogenic (trauma to the spine).
- **Chronic hypotension**; often associated with disease of the adrenals (Addison's disease).

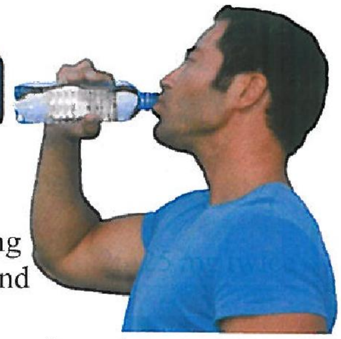
➢ Diagnosis:-



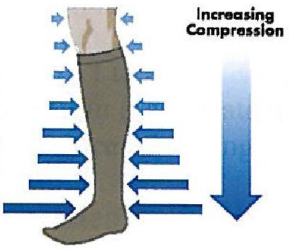
- **Blood pressure test.**
- **Blood tests**; shows blood sugar level and anemia.
- **Electrocardiogram (ECG)**; shows irregularities in heart rhythm.
- **Echocardiogram**; ultrasound of chest, shows detailed images of for heart structure and function.
- **Tilt table test** ***for orthostatic hypotension***; which evaluates how body reacts to changes in position (*see photo*).

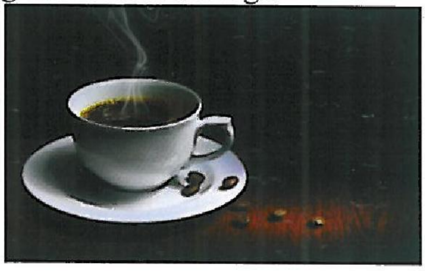
➢ Treatments:-

Lifestyle Modification



- **Drink enough amount of water**; to increase blood volume.
- **Add more salt in diet**; to increase blood volume.
- **Eat healthy diet**; contains all nutrients for good health by focusing on a variety of foods, including whole grains, fruits, vegetables, and lean chicken and fish.
- **Eat small, low-carbohydrate meals**; to help prevent blood pressure from dropping sharply after meals.
- **A morning dose of caffeine**; as coffee or tablet form can be effective.
- **Stand up gradually**; to reduce the dizziness and lightheadedness.
- **Avoid standing for long periods of time**; to prevent neurally mediated hypotension.
- **Wear compression stockings**; to reduce the pooling of blood in the legs.





Antihypotensive Drugs

➢ Antihypotensive Agents:-

- *Also known as* a **vasopressor agents**.
- *Classes*;
  - **Sympathomimetic Agents**; vasoconstrictors or cardiac stimulants.
  - **Synthetic Mineralocorticoids**; increase sodium and water retention.

Sympathomimetic Agents

Etilefrine (Effortil®)

- **Etilefrine** [ET-ele-FREEN] is a cardiac stimulant used as an antihypotensive, suggesting to stimulation of both α and β adrenergic receptors.
- *Used* for **symptomatic treatment of orthostatic hypotension (OH)**.
- *Dosage forms*; oral solution (drops), tablets and injection.
- Oral solution (10 drops = about 5 mg) should be taken with liquid before meals;
  - Under 2 years: 2-5 drops three times a day.
  - 2-6 years: 5-10 drops three times a day.
  - Over 6 years: 10-20 drops three times a day.

Midodrine (Gutron®)

- **Midodrine** [MIH-doe-DREEN] is a prodrug that is hydrolysed to **Desglymidodrine**.
- Desglymidodrine, is an α_1-agonist, ***does not*** stimulate cardiac β-adrenergic receptors.
- It is ***used*** orally for **symptomatic treatment of orthostatic hypotension (OH).**
- ***Dose***; adult, 10 mg orally three times a day. Do not give more frequently than every 3 hours, after the evening meal, or less than 4 hours before bedtime. Because desglymidodrine is excreted renally, dosing in patients with abnormal renal function should be cautious, it is recommended that treatment of these patients be initiated using 2.5-mg doses.

Heptaminol (Corasore®)

- **Heptaminol** [he-PTA-mee-nol] is a cardiac stimulant drug, it have a positive inotropic action, with a slight peripheral vasoconstrictor properties.
- ***Uses***; **hypotension, fainting tendency** and **circulatory collapse**.
- ***Dose***;
    - **Infants and children under 12 years**: 4-16 drops (25-100 mg) depending on age, 2-4 times daily, up to 6 times daily if necessary.
    - **Children over 12 years and adults**: One tablet or 25 drops, (150 mg) 2-4 times daily, up to 6 times daily if necessary.
- ***Pregnancy***; No data available.

Sympathomimetic agents used in hypotensive shock

- **Epinephrine** (*page no.* 56); ***used in*** anaphylactic shock.
- **Norepinephrine** (*page no.* 60), **Dopamine** (*page no.* 61) and **Dobutamine** (*page no.* 62); ***used in*** cardiogenic and septic shock.

Synthetic Mineralocorticoids

Fludrocortisone (Astonin-H®)

- **Fludrocortisone** [FLOO-droe-KOR-ti-sone] (also called 9α-fluorocortisol or 9α-fluorohydrocortisone) is a synthetic corticosteroid with moderate glucocorticoid potency and much greater mineralocorticoid potency.
- It is ***used*** primarily to replace the missing aldosterone hormone in **adrenal insufficiency** (Addison's disease), it cause ↑ salt and water retention ⇨ ↑ blood volume ⇨ ↑ CO ⇨ ↑ BP.
- ***Used with caution*** in diabetes mellitus, CHF, glaucoma, children and pregnancy.
- Most common ***side effects***; ankle edema, hypokalemia, headache and rarely congestive heart failure.
- ***Dose***; 0.05 to 0.1 mg orally/24 hours.

➢ **N.B:-**

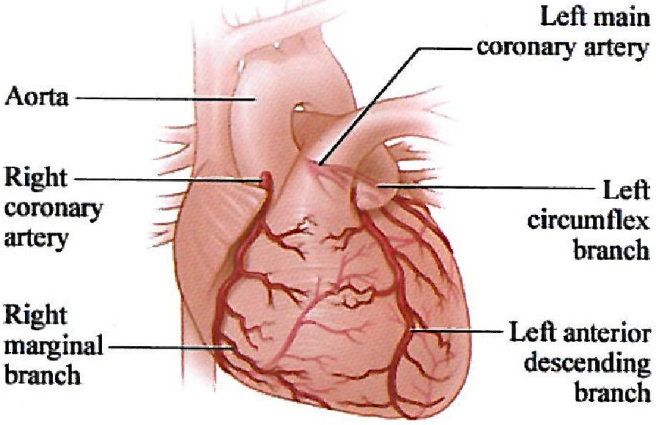
- **Anemia, infections** or **dehydration** must be treated firstly.
- **Administration of fluid and sodium chloride** to supplement volume expansion.
- **Vasopressin analogues** (**Desmopressin**; see endocrine chapter) may be used to supplement volume expansion.

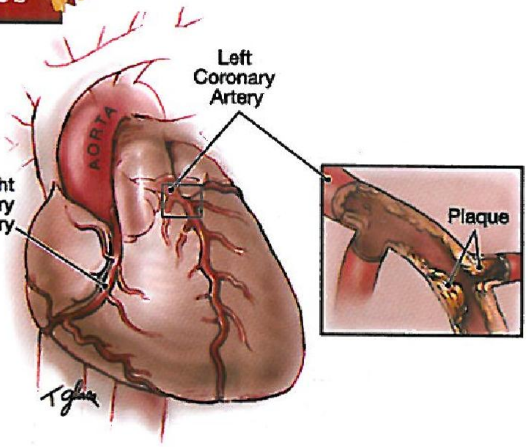
Coronary Heart Disease (CHD)

- **Coronary Heart Disease (CHD) or Coronary Artery Disease (CAD)**; also known as **ischemic heart disease (IHD), atherosclerotic heart disease, atherosclerotic** and **cardiovascular disease**; is a group of heart diseases that includes: stable angina, unstable angina, myocardial infarction, and sudden coronary death.
- **Ischemic Heart Disease (IHD)**; is one of the most common cardiovascular disease in developed countries and **angina pectoris** is the most common condition involving tissue ischemia.
- ***In*** 2013 **Coronary Artery Disease (CAD)** was ***the most common cause of death globally***, resulting in 8.14 million deaths (16.8%) up from 5.74 million deaths (12%) in 1990.

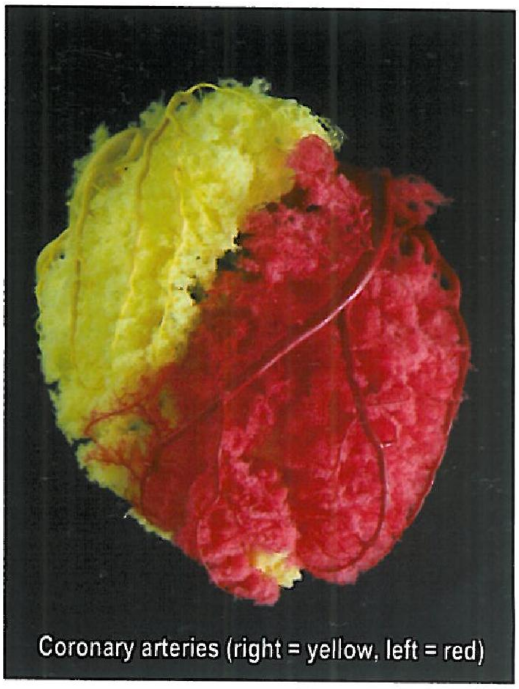
➢ Coronary Anatomy and Blood Flow:-

Coronary Arteries





- ***Coronary circulation***; is the circulation of blood in the blood vessels of the heart muscle (myocardium).
- The vessels that deliver oxygen-rich blood to the myocardium are *known as* **coronary arteries.**
- The major vessels of the coronary circulation are (1) the **left main coronary** that ***divides into*** **left anterior descending** and **circumflex branches**, and (2) the **right main coronary artery**.
- The left and right coronary arteries originate at the base of the aorta from openings called the **coronary ostia** located behind the aortic valve leaflets.
- The left and right coronary arteries and their branches lie on the surface of the heart.
- These vessels distribute blood flow to different regions of the heart muscle.
- When the vessels are not diseased, they have a low vascular resistance relative to their more distal and smaller branches that comprise the microvascular network.

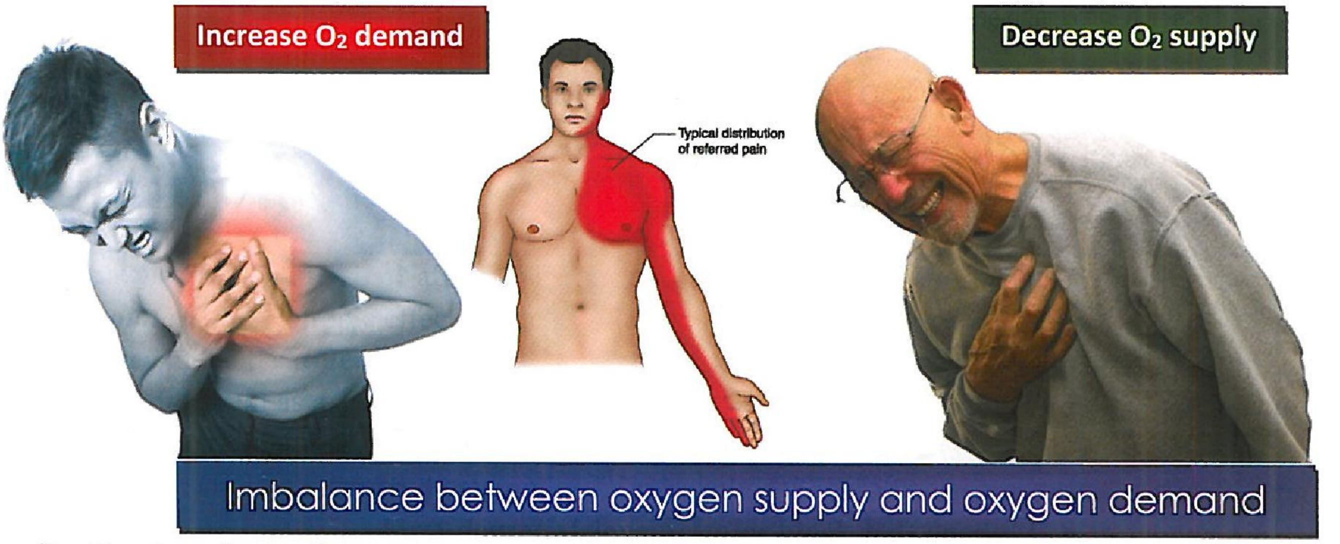

Coronary arteries (right = yellow, left = red)

- The heart regulates the amount of vasodilation or vasoconstriction of the coronary arteries based upon the oxygen requirements of the heart (oxygen demand).
- ***Failure of oxygen delivery*** caused by a ***decrease*** in **blood flow** in front of ***increased*** **oxygen demand** of the heart *results* in **tissue ischemia**, a condition of oxygen deficiency.
- Brief **ischemia** is ***associated*** with **intense chest pain, *known as* angina. Severe ischemia** can cause the **heart muscle to die** from hypoxia, such as during a **myocardial infarction**.

Angina Pectoris

➢ Background:-

- **Angina** [an-JIE-nuh or AN-juh-nuh], the term derives from the Latin **angere** "**to strangle**" and **pectus** "**chest**", and can therefore be translated as "**a strangling feeling in the chest**", *commonly known as* **angina**.
- ***Definition***; **Chest pain** caused by transient myocardial ischemia due to an imbalance between myocardial oxygen supply and oxygen demand.
- **Angina is not a disease**; **it is a symptom** of an underlying heart problem and is usually a **symptom of coronary heart disease** (CHD).

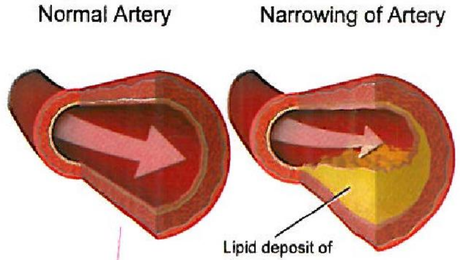

Increase O₂ demand
Typical distribution of referred pain
Decrease O₂ supply
Imbalance between oxygen supply and oxygen demand

➢ Angina Symptoms:-

- ***Angina pain***; Sudden, severe, pricking chest pain radiating to the neck, jaw, back and arms.
- ***Other symptoms***; Nausea, fatigue, shortness of breath, sweating and dizziness.
- ***N.B***; the severity, duration and type of angina can vary.

➢ Angina Risk Factors:-

- Coronary heart disease.
- Family history of heart disease.
- Unhealthy cholesterol levels.
- Unhealthy diet (high fat and high salt).
- Smoking.
- Diabetes.
- Inactivity.
- High blood pressure.
- Overweight or obesity.
- Stressful lifestyle.
- Age (Men > 45 years - Women > 55 years).

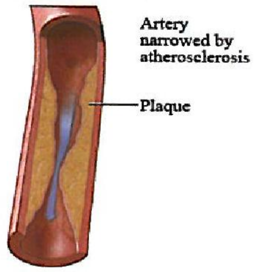
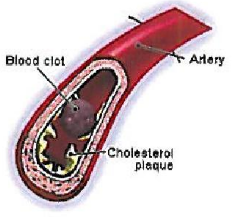
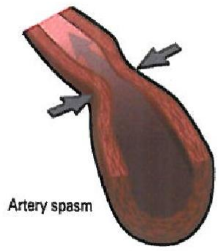

Normal Artery
Narrowing of Artery
Lipid deposit of plaque

- *N.B*; **Atherosclerosis**, or **hardening of the arteries**; is a condition in which plaque builds up inside the arteries. Plaque is made of cholesterol, fatty substances, cellular waste products, calcium and fibrin.

➢ Angina Types:-

- Stable Angina (Angina Pectoris).
- Unstable Angina.
- Variant (Prinzmetal's) Angina.
- Microvascular Angina (Cardiac syndrome X).

- *Brief Comparison*;

	Stable Angina	Unstable Angina	Variant Angina
Other Names	- Classical Angina. - Typical Angina. - Exertional or Effort Angina.	- Crescendo Angina. - Pre-infarction Angina. - Acute Coronary Syndrome.	- Vasospastic Angina. - Prinzmetal's Angina. - Angina Inversa.
Causes	- Narrowing of coronary arteries due to atherosclerosis. 	- Narrowing of coronary arteries due to atherosclerosis, transient formation of a blood clot within a coronary artery, result, total or near-total blockage. 	- Results from coronary vasospasm, which temporarily reduces coronary blood flow. 
Distribution	- Most common type.	- Common.	- Rare (2% of angina cases).
Occurs	- Physical exertion. - Emotions. - Exposure to cold weather. - Heavy meals.	- At rest or minimal exertion.	- At rest between midnight (12:00) and early morning (8:00). - Cold weather and stress can cause spasm.
Attack	- Usually lasts a short time (5 minutes or less).	- More severe and lasts longer, maybe as long as 30 minutes.	- Lasts from 5-30 minutes.
Relief	- Decreases at rest. - Relieved by nitroglycerin.	- Not relieved by rest. - Not relieved by nitroglycerin. - Treated as an emergency.	- Relieved by nitroglycerin.

- ***Other Types***;
  - **Microvascular Angina (Cardiac Syndrome X)**:
    - Is a symptom of coronary microvascular disease (MVD).
    - Affects the heart's smallest coronary artery blood vessels.
    - ***Occurs***; during spasms within the walls of these very small arterial blood vessels causes reduced blood flow to the heart muscle leading to a type of chest pain.
    - ***Symptoms***; chest pain usually lasts longer than 10 minutes, and it can last longer than 30 minutes.
  - **Woman's Angina**:
    - Women's symptoms make angina harder to detect.
    - A woman's angina symptoms can be different from the classic angina symptoms.
    - Angina in women often presents as weakness, fatigue, shoulder, stomach or back pain or shortness of breath.

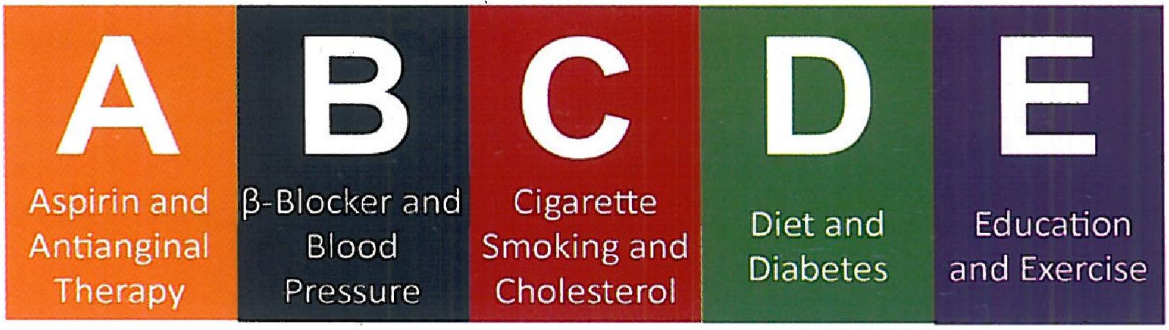
➢ Angina Diagnosis:-

- **Electrocardiogram (ECG)**; to detects and records the heart electrical activity.
- **Stress Test**; during exercise at increasing rates of exertion (generally by running on a treadmill); ECG will monitor heart rhythm.
- **Nuclear Stress Test**; a radioactive substance (*like* **thallium**) is injected into bloodstream, this substance mixes with blood and travels to the heart, a special scanner, which detects the radioactive material flow in the heart.

- **Cardiac Computerized Tomography (CT) Scan**; is a combines multiple X-ray images,
  A) Calcium-score screening heart scan; Show how much calcium is in the arteries, the level of calcium can help to show whether have coronary artery disease.
  B) Coronary CT Angiography (CTA); high-resolution, 3-dimensional pictures of the moving heart and great vessels.
- **Non-specific Tests**; blood pressure, lipid profile and kidney function test.

➢ Angina Treatment Goals:-

- ***The main goals*** of treatment in angina pectoris are to **relieve the symptoms**, **slow the progression of disease**, and **reduce the possibility of future events**, especially **myocardial infarction** (MI) and **premature death**.
  - ***Increase* O_2 Supply**; Vasodilators (Nitrates and Ca^{2+} Channel Blockers).
  - ***Decrease* O_2 Demand**; β-adrenergic Receptor Antagonists.
  - **Lifestyle modification.**
  - **Treat coronary artery disease;**
    - Decrease bad cholesterol level (LDL) e.g. statins (page no. 238)
    - Surgical procedures e.g. angioplasty.
- **Chronic stable angina and coronary heart disease (CHD) mnemonic;**



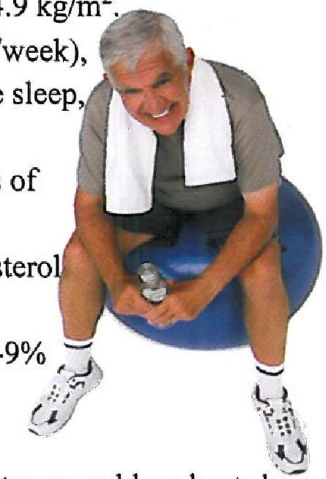
A	B	C	D	E
Aspirin and Antianginal Therapy	β-Blocker and Blood Pressure	Cigarette Smoking and Cholesterol	Diet and Diabetes	Education and Exercise

➢ Treatments Classification:-

- **Lifestyle Modification (General Measures).**
- **Drug Treatments (Antianginal Drugs).**
- **Coronary Artery Revascularization.**

Lifestyle Modification

- **No smoking** and **no environmental exposure to smoke.**
- **Weight reduction**; maintenance to a body mass index of 18.5-24.9 kg/m^2.
- **Physical activity**; 30-60 minutes every day (minimum of 5 days/week), increase physical activity is a great way to reduce stress, improve sleep, lose weight, and improve overall sense of wellbeing.
- **Diet**; eat a healthy diet with limited amounts of saturated fat, lots of whole grains, and many fruits and vegetables.
- **Cholesterol level and blood pressure**; maintenance LDL cholesterol less than 100 mg/dL, and BP less than 140/90 mm Hg.
- **Diabetes**; maintenance a glycosylated hemoglobin (A1c) of 7%-9% and avoid rosiglitazone in the treatment (see page no, 940).
- **Alcohol**; alcohol consumption should be limited.
- **Avoid angina triggers;** Physical exertion, emotional stress, extreme cold or heat, heavy meals, alcohol consumption and cigarette smoking.



Antianginal Drugs

- Four types of drugs, used either alone or in combination, are commonly used to manage patients with stable angina.
- Antiplatelet therapy and lipid-lowering therapy are needed to prevent clot formation and decrease atherosclerosis plaque formation.

Organic Nitrates

β-Blockers

Ca^{2+} Channel Blockers

New Antianginal Drugs

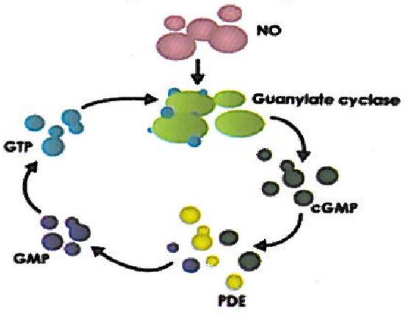
1) Organic Nitrates

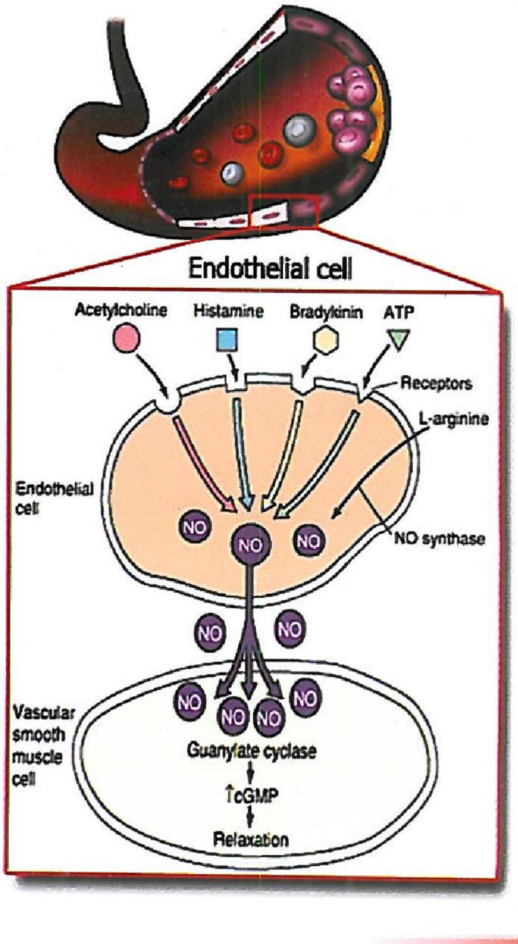
Nitroglycerin (NitromAck®)	**Isosorbide Mononitrate** (Effox®)
Isosorbide Dinitrate (Isordil®)	**Amyl Nitrate**

- Organic nitrates have been used for more than 100 years, and are still an important class used in the treatment of angina pectoris.
- **Nitroglycerin** (**NTG**) (**Glyceryl Trinitrate**; **GTN**) [nye-troe-GLIS-er-in] is the prototype of these group, **Isosorbide** [eye-soe-SOR-bide] **Dinitrate** (**ISDN**), **Isosorbide-5-Mononitrate** (**5-ISMN**) and **Amyl Nitrate** [A-mil NYE-trite] (highly volatile liquid which is administered by inhalation) are simple nitric and nitrous acid esters of polyalcohols.

Mechanism OF Action

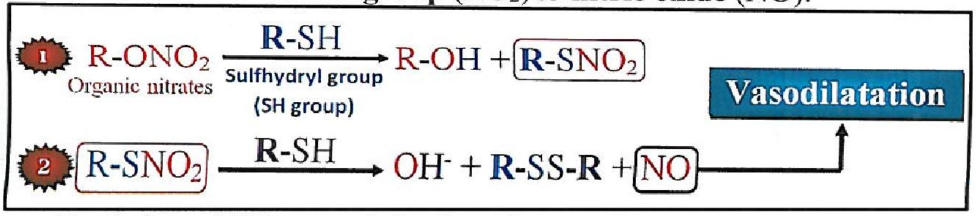
- ***Normally***;
  - ***Endogenous*** **nitric oxide** (**NO**) is primarily produced by vascular endothelial cells, which cause relaxation of vascular smooth muscle.
  - **NO** ☞ act by ***stimulation*** of **guanylate cyclase**, lead to ***increase*** **cyclic guanosine monophosphate** (**cGMP**), which subsequently ***cause*** **vascular smooth muscle relaxation** through several possible mechanisms; ***decrease*** **Ca^{2+} influx** and **K^+ channels** ***activation***, (hyperpolarization).


NO
Guanylate cyclase
GTP
cGMP
GMP
PDE


Endothelial cell
Acetylcholine
Histamine
Bradykinin
ATP
Receptors
L-arginine
Endothelial cell
NO
NO synthase
Vascular smooth muscle cell
Guanylate cyclase
↑cGMP
Relaxation

Mechanism OF Action

- **Organic Nitrates**;
  - **Organic nitrates** are drugs that ***not directly*** **release** or **synthesis** of endogenous NO within tissues.
  - **Nitrate group** (**NO_2**) in organic nitrate ***interact*** with **enzymes** (nitric oxide synthase) and intracellular **sulfhydryl group** (R-SH) (**SH group**) that ***reduce*** the **nitrate group** (NO_2) ***to*** **nitric oxide** (**NO**).


1
$R\text{-}ONO_2 \xrightarrow[\text{Sulfhydryl group (SH group)}]{R\text{-}SH} R\text{-}OH + \boxed{R\text{-}SNO_2}$
Organic nitrates
2
$\boxed{R\text{-}SNO_2} \xrightarrow{R\text{-}SH} OH^- + R\text{-}SS\text{-}R + \boxed{NO}$
Vasodilatation

  - Depletion of SH group ⇨ lead to **nitrate tolerance.**
  - **Sildenafil** (see page no; 76) is selective inhibitors of Phosphodiesterase type 5 (PDE-5) which is responsible for degradation of cGMP into GMP ⇨ accumulation of cGMP ⇨ VD of penis ☞ Erection.

Pharmaco Kinetics

- The liver contains a high-capacity organic reductase, which sequentially removes nitrate groups from the parent drug, and ultimately inactivate the drug, ***so*** hepatic first-pass metabolism is high and oral bioavailability is very low for the traditional organic nitrates, nitroglycerin (GTN) and isosorbide dinitrate (ISDN).

- Sublingual administration, which avoids the first-pass effect, is therefore preferred for administration of GTN and ISDN.

- **Pharmacokinetics properties**:

	GTN	ISDN	ISMN
Oral Bioavailability	Less than 1%	About 22%	Nearly 100%
Protein Binding	Moderate	Very low	Very low
Biotransformation	Hepatic (very rapid and nearly complete) and in blood (enzymatically)		
Half-life	Sublingual: 3 min.	Sublingual: 1 hour	Oral: 5 hours
Onset of action	Sublingual: 1-3 min.	Sublingual: 2-5 min.	Oral: 1 hour
Duration of action	Sublingual: 30-60 min. SR formula: 8 to 12 h.	Sublingual: 1-2 h. Oral tablets: 4-6 h.	Oral: 12 hours
Elimination	Renal (after nearly total metabolism)		

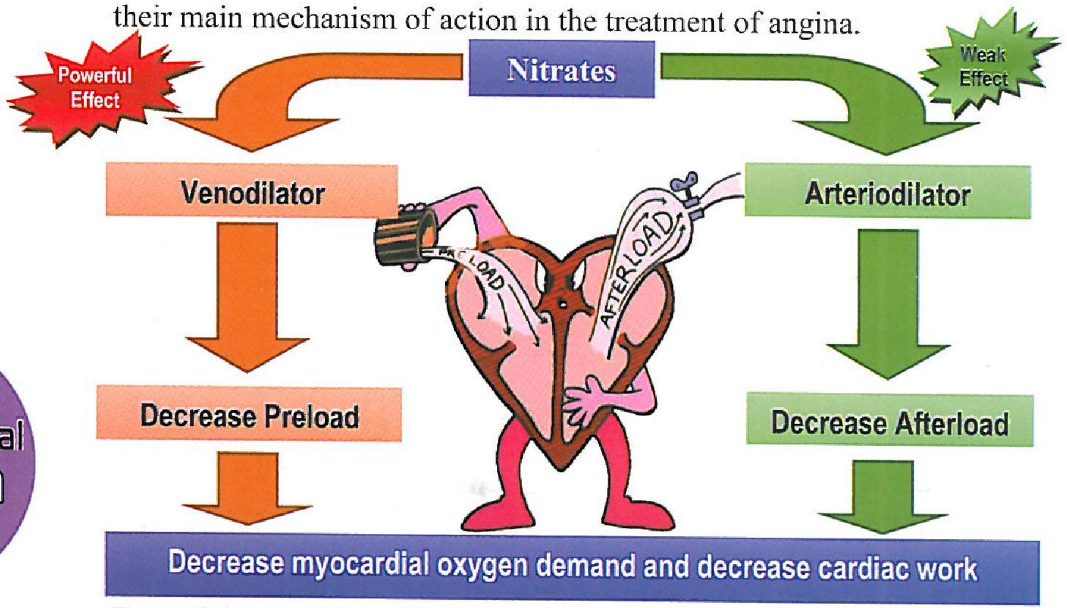
- **Pharmaceutical Preparations** and **Doses**:
  - *Short Acting* (Acute Attacks):
    - **Nitroglycerin**;
      - **IV**; 5 mcg/min continuous IV infusion via non-absorptive tubing; increase by 5 mcg/min every 3 to 5 minutes as needed up to 20 mcg/min, then by 10 or 20 mcg/min if needed. N.B; Starting doses of 25 mcg/min or higher have been used with polyvinyl chloride (PVC) tubing.
      - **Lingual Spray**; 1 to 2 sprays (0.4 to 0.8 mg) on or under tongue every 5 minutes as needed, up to 3 sprays in 15 minutes.
      - **Sublingual Tablet**; 0.3 to 0.6 mg sublingually or in the buccal pouch every 5 minutes as needed, up to 3 doses in 15 minutes.
    - **Isosorbide Dinitrate**;
      - **Sublingual Tablet**; 2.5-5 mg every 2 to 3 hours.
    - **Amyl Nitrite**;
      - **Inhalation**; 0.3 milliliter (1 ampule) taken by inhaling the vapour of amyl nitrite through the nose. Dose may be repeated within 1 to 5 minutes if pain is not relieved.

Pharmaco Kinetics

- *Long Acting* (Angina Prophylaxis):
  - **Nitroglycerin**;
    - **Extend Release Capsule**; 2.5 to 6 mg orally 3 to 4 times a day.
    - **Topical Ointment**; 1/2 inch or 1.27 cm (7.5 mg) topically on rising in the morning and 1/2 inch (7.5 mg) 6 hours later.
    - **Transdermal Patch**; 0.2 to 0.4 mg/hr., patch applied topically once a day for 12 to 14 hours per day (patch-off period of 10-12 hours).
  - **Isosorbide Dinitrate**;
    - **Immediate Release**; initial: 5-20 mg orally 8-12hr, maintenance: 10-40 mg orally 8-12hr.
    - **Extended Release**; initial: 40 mg orally, maintenance: 40-80 once or twice daily.
    - **Sublingual Tablet** (***Prophylaxis***): 2.5-5 mg 15 minutes before performing activities likely to cause angina.
  - **Isosorbide Mononitrate**;
    - **Immediate Release**; 20 mg orally twice a day.
    - **Extended Release**; 30 to 60 mg orally once a day in the morning.

Pharmacological Action

- **GTN** ***relaxes*** all types of smooth muscle regardless of the cause of the pre-existing muscle tone. It has practically no direct effect on cardiac or skeletal muscle.
- **Nitrates** ***cause*** **dilation of veins** ***predominates*** over that of arterioles, dilation of the large veins, which reduces preload (venous return to the heart) and, therefore, reduces the work of the heart. This is believed to be their main mechanism of action in the treatment of angina.



- ***Powerful*** **venodilator** and ***increase*** venous capacitance ☞ ***decrease*** **ventricular preload.**
- ***Weak*** **arteriodilator** ☞ ***decrease*** **afterload** (minimal effect).
- ***Reduction in preload and afterload lead to***;
  - ***Decrease*** myocardial oxygen demand.
  - ***Decrease*** cardiac work (decrease CO).
- **Effects on coronary blood flow**;
  - Organic nitrates can relax vasospastic coronary arteries.
  - They have little or no effect on total coronary blood flow in patients with typical angina due to atherosclerosis.
- **Other actions (minimal effect)**;
  - Inhibit platelet aggregation (due to increase cGMP level).
  - Spasmolytic effect (smooth muscle relaxation).
  - Nitrite ion react with hemoglobin to produce methemoglobin.

Side Effects

** Vasodilation Related Side Effects **

- ***The major acute adverse effects of organic nitrates are***:
  - Orthostatic hypotension (dizziness or syncope).
  - Throbbing headache (Cerebral vasodilation).
  - Reflux tachycardia.
  - Facial flushing.

** Nitrate Tolerance **

- Continuous or frequent exposure to organic nitrates may lead to the development of complete tolerance (tachyphylaxis).
- Tolerance does not occur equally with all nitric oxide donors.
- The mechanisms by which tolerance develops are not fully understood.
- **Nitrate Tolerance Hypothesis**;
  - Depletion of SH group.
  - Excessive generation of free radicals.
  - Dysfunction of endothelial nitric oxide synthase.
  - Decrease sensitivity of guanylate cyclase.
  - Activation of renin-angiotensin aldosterone axis.

☞ **Avoid Nitrate Tolerance**;

1: **Nitrate holiday** (**"nitrate free period"** or **NFP**) of at least 10 hours and preferably up to 14 hours is recommended to avoid tolerance;

- *For example;*
  - Regular-release isosorbide dinitrate, which is administered 3-4 times daily, may be scheduled at 7:00 AM, Noon, and 5:00 PM.
  - Isosorbide-5-mononitrate and sustained release preparations of nitroglycerin or isosorbide dinitrate may be given twice daily at 8:00 AM and 3:00 PM, allowing a 10-12 hour nitrate holiday.
  - Removal of nitroglycerin ointment paper and residual ointment at bedtime.
  - A nitroglycerin transdermal patch placed at 8:00 AM may be removed at bedtime.

2: **Sulfhydryl group donors** like **N-acetylcysteine** (**NAC**) and **L-methionine** have been shown to potentially reduce nitrate tolerance, but they may potentiate the effects of nitrates.

3: Oral **vitamin C**, **vitamin E** (antioxidants) and **folic acid** may be effective in ameliorating nitrate tolerance.

4: **Carvedilol** (antioxidant properties) and **Nebivolol** (antioxidant properties and NO-mediated vasodilatory effects) may reduce nitrate tolerance associated with continuous nitrate therapy.

- ***Recent study***;
  - ACEIs and ARBs may be effective in nitrate tolerance.
  - Animal studies have demonstrated that statins may be able to prevent nitrate tolerance.

** Monday Syndrome or Monday Morning Sickness **

- Workers in nitroglycerin manufacturing, who are experiencing to regular nitroglycerin exposure in the workplace, leading to the development of tolerance for the vasodilating effects.
- Over the weekend, the workers lose the tolerance and, when they are re-exposed on Monday, the drastic vasodilation produces a fast heart rate, dizziness, and a headache "Monday morning headache".

- ***Drug Interaction***;
  - **Sildenafil**, **Tadalafil** and **Vardenafil** increase the blood pressure lowering effects of nitrates and may cause excessive blood pressure reduction.

- ***Pregnancy***;
  - Category C, should be given to pregnant women only if clearly needed.

- ***Beneficial and deleterious effects of nitrates in treatment of angina***;

Effect	Result
Potential beneficial effects;	
- Decreased ventricular volume, - Decreased arterial pressure, - Decreased ejection time.	- Decreased myocardial oxygen requirement.
- Vasodilatation of epicardial coronary artery.	- Relief of coronary artery spasm.
- Increased collateral flow.	- Improved perfusion to ischemic myocardium.
- Decreased left ventricular diastolic pressure.	- Improved subendocardial perfusion.
Potential deleterious effects;	
- Reflex tachycardia - Reflex increase in contractility	- Increased myocardial oxygen requirement.
- Decreased diastolic perfusion time due to tachycardia	- Decreases coronary perfusion.

- ***Mechanism of Clinical Effect***;
  - **A) Nitrate Effects in Angina Effort**;
    - Reduction in oxygen consumption is the major mechanism for the relief of effort angina.
  - **B) Nitrate Effects in Variant Angina**;
    - Relaxing the smooth muscle of epicardial coronary arteries and relieving coronary artery spasm.
  - **C) Nitrate Effects in Unstable Angina**;
    - Nitrates are also useful in the treatment of the acute coronary syndrome of unstable angina, but mechanism for their beneficial effects is not clear.
- ***Finally***; Nitrates are effective in stable, unstable, and variant angina.

2) β-Adrenoceptor Antagonists (β-blockers)

- Although they are ***not* vasodilators** (with the exception of **Carvedilol** and **Nebivolol**), β-blocking drugs are ***extremely* useful in the management of effort angina.**

- The ***beneficial* effects** of β-blocking agents are related to their ***hemodynamic effects***;
  - ***Decreased* heart rate, blood pressure** and **contractility** ⇨ ***Decrease* myocardial oxygen requirements at rest and during exercise.**
  - ***Lower* heart rate** is also associated with an ***increase*** in **diastolic perfusion time**, may ⇨ ***Increase* coronary perfusion.**

** **β-blockers** ***reduce*** the **risk of death** and **MI** in patients who have had a prior MI and ***also improve*** **mortality** in patients with **hypertension** and **heart failure** with reduced ejection fraction.

- Agents with **intrinsic sympathomimetic activity (ISA)** such as **Pindolol** ***should be avoided*** in patients with angina and those who have had a MI.

- **β-blockers** ***should be avoided*** in patients with **severe bradycardia**.

- ***Cardioselective* β-blockers** can be **used in patients** with **diabetes, peripheral vascular disease,** and **chronic obstructive pulmonary disease** (**COPD**), as long as they are monitored closely.

- ***Nonselective* β-blockers** should be ***avoided*** in patients with **asthma** or **COPD**.

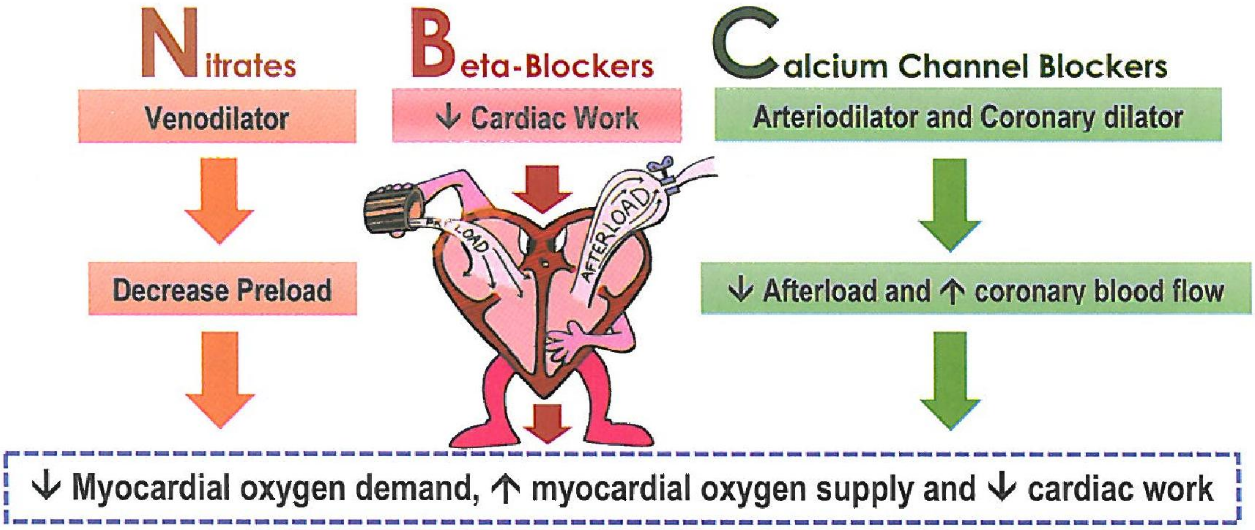
- **The β-blockers must be tapered off gradually** over 2 to 3 weeks to avoid rebound angina, MI, and hypertension.

- **β-blocker** ***not used*** with **non-dihydropyridines Ca^{2+} channel blockers** (**Verapamil** and **Diltiazem**) to avoid heart block.

- **Carvedilol** > **Metoprolol Succinate** > **Bisoprolol** are ***only*** **β-blockers** ***may be used*** in **CHF**.
- ***See* ANS *Chapter***; page no 79; for more information.

3) Calcium Channel Blockers (CCBs)

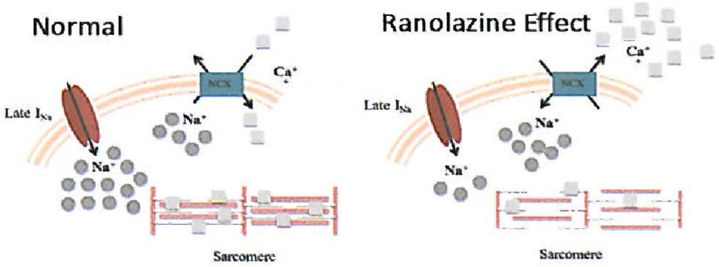
- *All* **calcium channel blockers** are **arteriolar vasodilators** that cause a ***decrease*** in **smooth muscle tone** and **vascular resistance**.
- These agents primarily ***affect*** the **resistance of peripheral** and **coronary arteriolar smooth muscle**.
- ***In the treatment of effort-induced angina***, calcium channel blockers ***reduce*** **myocardial oxygen consumption** by ***decreasing*** **vascular resistance** ⇨ ***decreasing*** **afterload**.
- Their efficacy in **vasospastic angina** is ***due to*** **relaxation of the coronary arteries**.
- **Verapamil** mainly affects the ***myocardium***, whereas **amlodipine** exerts a greater effect on ***smooth muscle in the peripheral vasculature***. **Diltiazem** is ***intermediate in its actions***.
- **CCBs** are ***useful*** in **patients** who also have **asthma**, **diabetes**, and/or **peripheral vascular disease**.
- ***Pharmacologic effects***;
  1) ***Decrease*** **coronary vascular resistance** and ***increase*** **coronary blood flow** (↑ **oxygen supply**).
  2) **(-ve) inotropic effect**, to varying degrees; **Verapamil** much greater than **Diltiazem** and **Amlodipine** (***decrease*** **oxygen demand**).
  3) ***Decrease*** **heart rate** (**Verapamil** and **Diltiazem** ***only***) ⇨ ***decrease*** **oxygen demand**.
- **Verapamil** and **Diltiazem** ***should be avoided*** in **patients with heart failure** or **with atrioventricular block** due to their -ve inotropic and -ve dromotropic effects.
- *See* page no 129; for more information.


Nitrates
Beta-Blockers
Calcium Channel Blockers
Venodilator
↓ Cardiac Work
Arteriodilator and Coronary dilator
PRELOAD
AFTERLOAD
Decrease Preload
↓ Afterload and ↑ coronary blood flow
↓ Myocardial oxygen demand, ↑ myocardial oxygen supply and ↓ cardiac work

4) Newer Antianginal Drugs

Ranolazine (Ranexa®)

- **Ranolazine** [ra-NOE-la-zeen] is a ***newer antianginal drug*** (first approved in 2006), classified as Na^+ channel blocker.
- Ranolazine has antianginal as well as antiarrhythmic properties.
- It is ***indicated for*** the ***treatment of*** **chronic angina** and may be used alone or in combination with other traditional therapies.

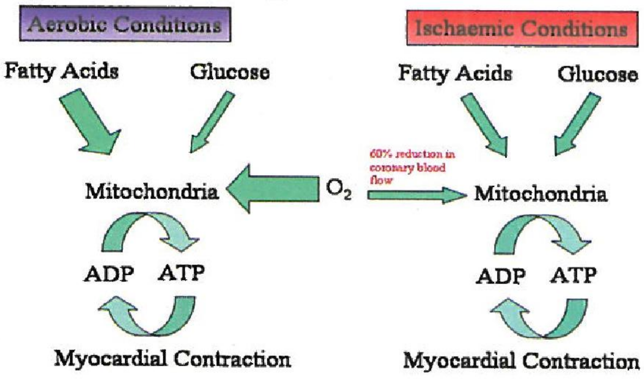

Normal
Ranolazine Effect
Late I_{Na}
NCX
Na^+
Ca^+
Sarcomere

- ***Mechanism of action***; ***inhibits*** the **late phase of the inward sodium channel** (**late I_{Na}**) in ischemic myocytes during repolarization ⇨ ***reduction*** in **intracellular sodium concentrations**. This reduction in sodium concentrations ⇨ ***reduced*** **calcium influx** (NCX = Na-Ca exchanger) which ***decreases*** **ventricular tension** and **myocardial oxygen consumption**.
- ***Dose***; 500 mg orally twice daily. ***May*** increase to 1 g twice daily, based on symptoms (max, 2g/day).
- ***Drug interactions***; **liver CYP$_3$A inhibitors** as **diltiazem**, **verapamil**, **erythromycin** and **grapefruit juice**, and **liver CYP$_2$D$_6$ inhibitors** as **tricyclic antidepressants** (dose; not exceed 500 mg).

- ***Most common side effects***; dizziness, headache, constipation and nausea.
- It ***can*** **prolong the QT interval** and ***should be avoided*** with other drugs that cause QT prolongation.
- ***Pregnancy***; Ranolazine has been assigned to pregnancy category C by the FDA.

Trimetazidine (Vastarel® MR)

- **Trimetazidine** (**TMZ**) [trye-META-zee-dine] is a **first cytoprotective anti-ischemic agent**.
- **Trimetazidine** is a clinically ***effective*** **antianginal agent** that has ***no*** **negative inotropic** or **vasodilator properties**.
- It is ***indicated*** in adults as add-on therapy for the symptomatic treatment of patients with **stable angina pectoris** who are inadequately controlled by or intolerant to first-line antianginal therapies.
- ***Dose***; 20 mg three times a day during meals or 35 mg twice daily during meals.
- ***Mechanism of action***;
  - It ***inhibits*** **beta-oxidation of fatty acids (pFOX inhibitor)** by ***blocking*** **long-chain 3-ketoacyl-CoA thiolase**, which ***enhances*** **glucose oxidation.**
    - **In an ischaemic cell**; energy obtained during glucose oxidation requires less oxygen consumption than in the beta-oxidation process.
    - ***Potentiation*** of **glucose oxidation** optimizes cellular energy processes, thereby ***maintaining*** **proper energy metabolism during ischemia.**



- ***Contraindication***; Parkinson disease and severe renal impairment (creatinine clearance < 30ml/min).
- ***Most common side effects***; dizziness, headache, abdominal pain, diarrhea, dyspepsia, nausea, vomiting and hypersensitivity reactions.

Nicorandil (Randil®)

- **Nicorandil** [Nik-oh-ran-dill] is a ***new organic nitrate with vasodilator properties.***
- It is an antianginal drug that has the ***dual properties*** of a **nitrate** and **potassium channel activators.**
- ***Mechanism of action***;
  - ***Nitrate***: stimulates guanylate cyclase to increase formation of cyclic GMP, decreasing the calcium influx, leads to smooth muscle vasodilation.
  - ***K^+ channel opener***: activates K^+-ATP channel, causing K^+ efflux. This hyperpolarizes the cell, which inactivates voltage-gated calcium channels and reduces free intracellular Ca^{2+}.
- ***Dose***; 10 mg twice daily, may increase this dose if necessary. Maximum dose is 30 mg twice daily.
- ***Most common side effects***; headaches, dizziness, flushing and reflex tachycardia.

Ivabradine (Procoralan®)

- **Ivabradine** [eye-VAB-ra-deen] it was approved by the European Medicines Agency (EMA) in 2005 and by the US FDA in 2015.
- It is ***indicated for*** the **symptomatic treatment of chronic stable angina pectoris** in patients with normal sinus rhythm who cannot take β-blockers or in combination with β-blockers in patients inadequately controlled with an optimal beta-blocker dose.
- It is ***also indicated*** in **combination *with* beta blockers** in **heart failure** patients with left ventricular ejection fraction lowers than 35% inadequately controlled by β-blockers alone and whose heart rate exceeds 70 beats per minute.
- ***Mechanism of action***; Heart rate is determined by spontaneous electrical pacemaker activity in the sinoatrial (SA) node controlled by the I_f current (I_f channel, f for "funny"), **Ivabradine** is **the first selective sinus node I_f channel inhibitor**, slowing the heart rate and allowing more time for blood to flow to the myocardium, ↓ the myocardial oxygen demand without effect on inotropic or BP.
- ***Dose***; The starting dose usually 5 mg twice daily. The maintenance dose usually 7.5 mg twice daily.
- ***If there is no improvement within 3 months***, **Ivabradine** should be discontinued.
- ***Most common side effects***; luminous phenomena or phosphenes (seeing light without light actually entering the eye), first-degree AV block, ventricular extrasystoles, dizziness and/or blurred vision.
- ***Drug interactions***; **Liver CYP$_3$A$_4$ inhibitors**, including azole antifungals, macrolide antibiotics, nefazodone and the antiretroviral drugs nelfinavir and ritonavir and with verapamil or diltiazem.

➢ N.B.;

- **Allopurinol**, a xanthine oxidase inhibitor (See page no. 477), an enzyme that contributes to oxidative stress and endothelial dysfunction, a recent study suggests that high-dose allopurinol (600 mg) prolongs exercise time in patients with atherosclerotic angina.
- **Antiplatelet therapy** (See page no. 220), ***for example***;
  - **Aspirin**;
    - Indicated in all patients with CHD unless contraindicated.
    - ***Dose***: 75-162 mg/day.
    - Decreases cardio vascular events by about one-third.
  - **Clopidogrel**;
    - A dose of 75 mg/day, may use in patients with an aspirin allergy.
- **Thrombolytic therapy** (See page no. 219); improve survival rates in patients with acute MI
- **Lipid-lowering therapy** (See page no. 237), e.g. Statins.
- **ACE inhibitors**; reduce total mortality, MI, stroke and heart failure among specific patients, including those with heart failure, previous vascular disease alone or high-risk diabetes.

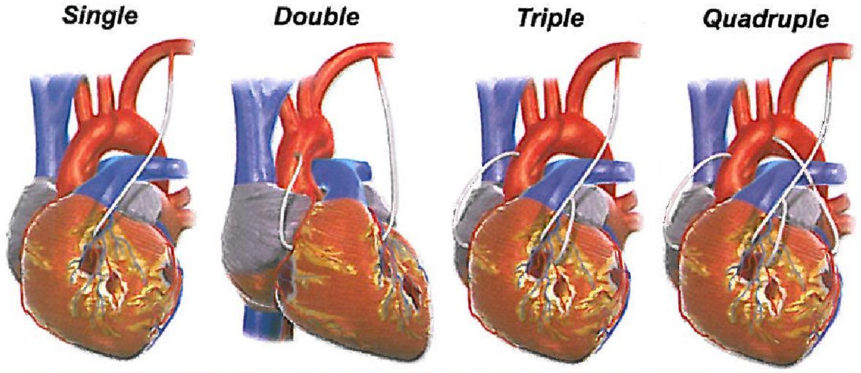
➢ Effects of antianginal agents in angina pectoris:-

	Nitrates alone	β-Blockers or CCBs	Nitrates + (BBs or CCBs)
Heart Rate	Reflex increase	Decrease	Decrease
Arterial Pressure	Decrease	Decrease	Decrease
End-diastolic volume	Decrease	Increase	None or Decrease
Contractility	Reflex increase	Decrease	None
Ejection time	Decrease	Increase	None

Coronary Artery Revascularization

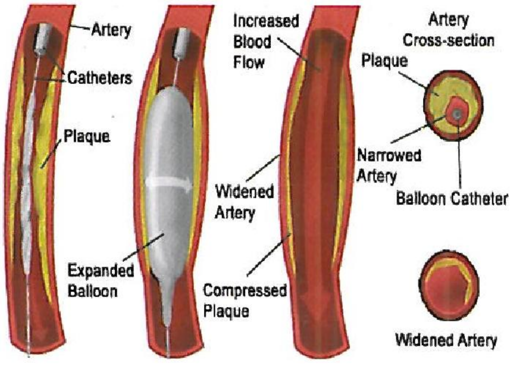
Coronary Artery Bypass Grafting (CABG)

- Bypass typically requires open-chest surgery. The surgical procedure places new blood vessels around existing blockages to restore necessary blood flow to the heart muscle.

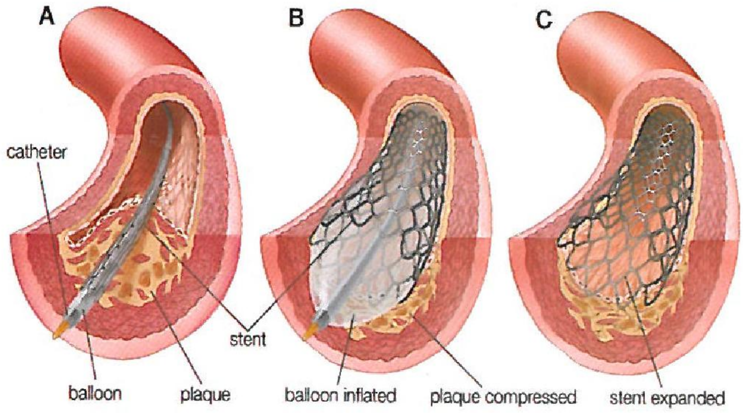


Coronary Artery Balloon Angioplasty

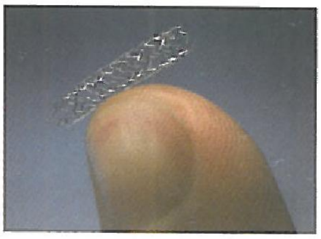
- It ***also called*** **Percutaneous coronary intervention (PCI)** Percutaneous transluminal coronary angioplasty (PTCA).
- In the late 1970s, doctors began using balloon angioplasty to treat narrowed coronary arteries.
- During this procedure, a very thin, long, balloon-tipped tube, called a catheter, is inserted into an artery in either the groin or arm and is moved to the site of the blockage with help from an X-ray.
- The balloon at the tip of the catheter is then inflated to compress the blockage and restore blood flow, and then it's deflated to allow the catheter and balloon to be removed.



Coronary Artery Stents


A
B
C
catheter
stent
balloon
plaque
balloon inflated
plaque compressed
stent expanded

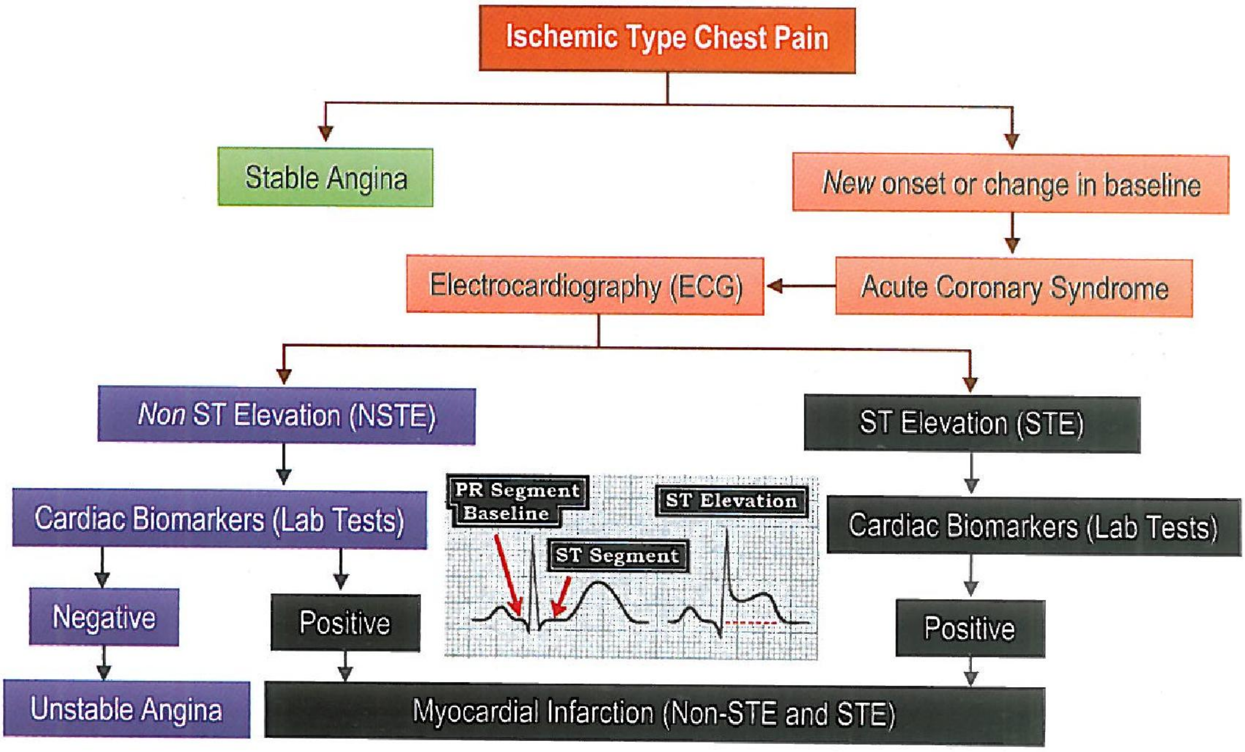
- A coronary stent is a tube-shaped device placed in the coronary arteries that supply blood to the heart, to keep the arteries open in the treatment of coronary heart disease.
- In 1986, French researchers implanted the first stent into a human coronary artery.
- In 1994, the FDA approved the first heart stent for use in the U.S.
- There are many types of coronary stent (Next page)
- ***Coronary stent types***;
  - **Bare-Metal Stent (BMS)**; Metallic stent without a coating.
  - **Drug-Eluting Stent (DES)**; Stent are coated with an antiproliferative drug, allows drug elution into the coronary wall for weeks after implantation.
  - **Bioresorbable stent**; Developed (2011) by Abbott (**Absorb®**), also called ***Abbott* Vascular Bioresorbable Vascular Scaffold** (**BVS**), stent dissolves after about two years.
  - **Dual-Therapy Stent**; **COMBO Stent®** is the only dual therapy stent available today, Developed (2013) by OrbusNeich, combines the **Genous technology** (endothelial progenitor cell; EPC) which promotes the accelerated natural healing of the vessel wall ***with*** an **antiproliferative**



Transmyocardial Laser Revascularization (TMLR)

- Transmyocardial Laser Revascularization (TMLR) is a type of surgery that uses a laser to make tiny channels through the heart muscle and into the lower-left ventricle.
- After TMLR, when oxygen-rich blood enters the left ventricle, some of that blood can flow through the tiny channels and carry much-needed oxygen to the starving heart muscle.
- During a typical procedure, approximately 10 –50 channels are made in each targeted region of the heart muscle.

➤ Clinical Manifestation:-

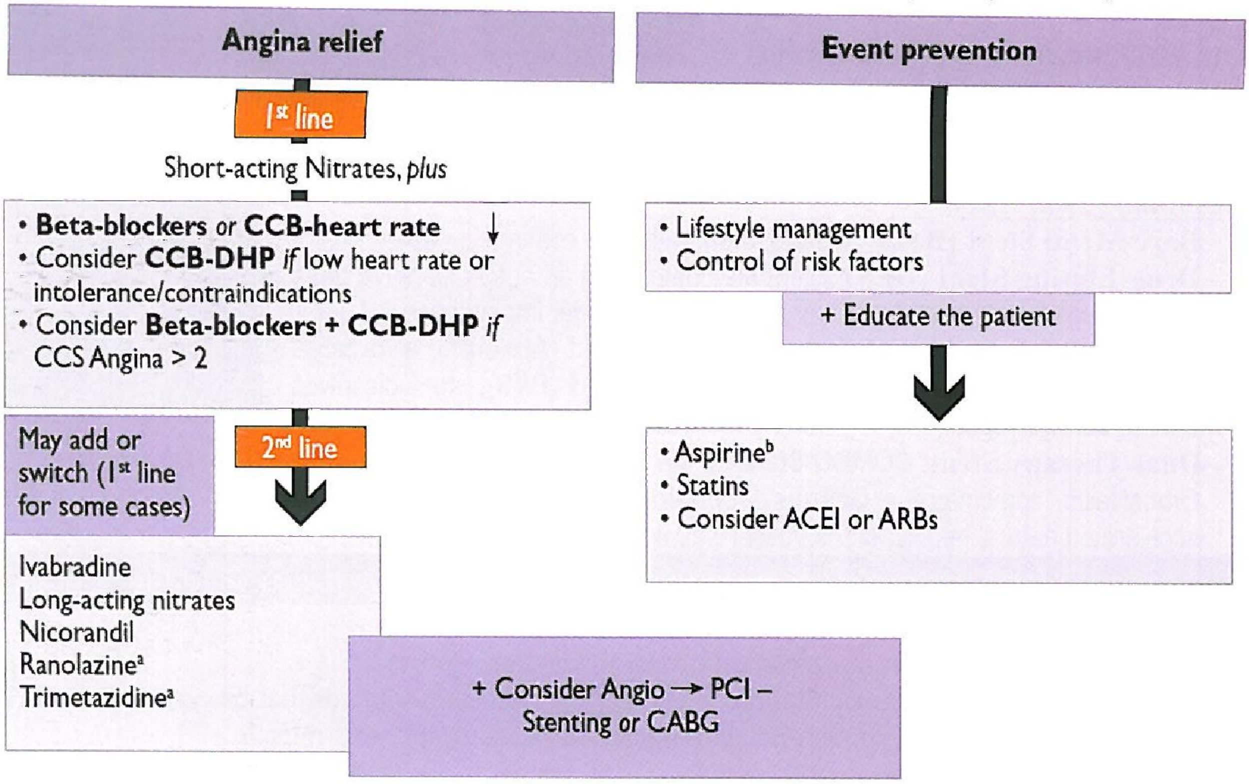

Ischemic Type Chest Pain
Stable Angina
New onset or change in baseline
Acute Coronary Syndrome
Electrocardiography (ECG)
Non ST Elevation (NSTE)
ST Elevation (STE)
Cardiac Biomarkers (Lab Tests)
Negative
Positive
Unstable Angina
PR Segment Baseline
ST Segment
ST Elevation
Cardiac Biomarkers (Lab Tests)
Positive
Myocardial Infarction (Non-STE and STE)

➢ Management of Acute Attack of Angina:-

- Dissolve one tablet of nitroglycerin under tongue or in buccal pouch at first sign of anginal attack, repeat every 5 min. until relief is obtain. (Don't; take more than 3 tablets per 15 min).
- If pain continues, patient should go to the hospital (ECG and cardiac biomarkers).

➢ Medical Management of Patients with Stable Coronary Artery Disease:-

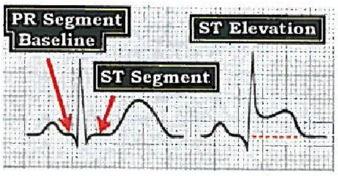
- *Notes from*; 2013 ESC guidelines on the management of stable coronary artery disease:-
  - Medical management of patients with stable coronary artery disease;


Angina relief
Event prevention
1st line
Short-acting Nitrates, plus
• Beta-blockers or CCB-heart rate ↓
• Consider CCB-DHP if low heart rate or intolerance/contraindications
• Consider Beta-blockers + CCB-DHP if CCS Angina > 2
May add or switch (1st line for some cases)
2nd line
Ivabradine
Long-acting nitrates
Nicorandil
Ranolazine^a
Trimetazidine^a
+ Consider Angio → PCI – Stenting or CABG
• Lifestyle management
• Control of risk factors
+ Educate the patient
• Aspirine^b
• Statins
• Consider ACEI or ARBs

- *Source*; 2013 European Society of Cardiology (ESC) guidelines on the management of stable coronary artery disease.
- **ACEI** = Angiotensin Converting Enzyme Inhibitor.
- **CCB** = Calcium Channel Blockers.
- **DHP** = Dihydropyridines.
- **CCS** = Canadian Cardiovascular Society.
- [a] = Data for diabetics.
- [b] = If Intolerance, consider Clopidogrel.
- **PCI** = Percutaneous Coronary Intervention.
- **CABG** = Coronary Artery Bypass Graft.

Acute Coronary Syndromes (ACSs)

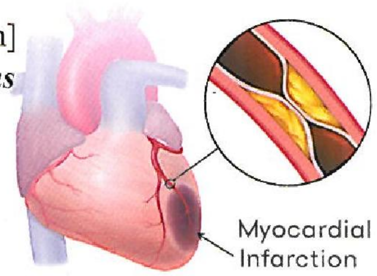
- **Acute coronary syndromes** (**ACSs**) are a spectrum of conditions compatible with acute myocardial ischemia or infarction due to sudden reduction in coronary blood flow.
- **ACSs** are ***classified according*** to **electrocardiographic** (**ECG**) **changes** into;
  1) **ST-segment elevation myocardial infarction** (**STEMI**).
  2) **Non-ST-segment elevation** (**NSTE**) **ACS**, *which includes;*
     A) **Non-ST-segment elevation myocardial infarction** (**NSTEMI**).
     B) **Unstable Angina** (**UA**).



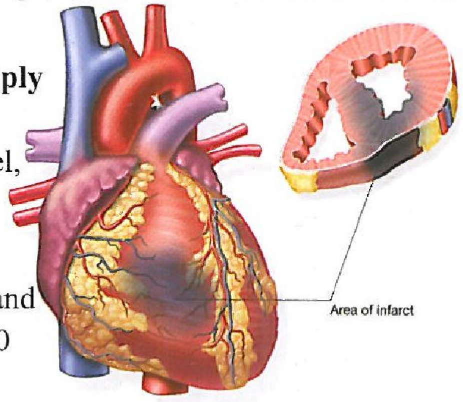
- **STEMI** is ***more severe*** enough to ***produce*** **myocardial necrosis** (complete block).
- **STEMI** is the combination of symptoms related to poor oxygenation of the heart with elevation of the ST segments on the ECG followed by an ↑ in proteins in the blood related to heart muscle's death.

Myocardial Infarction (MI)

➢ Background:-



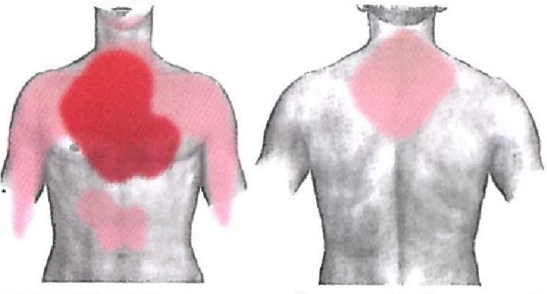
- **Myocardial infarction** [my-oh-KAR-dee-ahl in-FARK-shun] or **acute myocardial infarction** (**AMI**), ***commonly known as*** a "**heart attack**".
- The word "**infarction**" comes from the Latin "**infarcire**" meaning "**stuffed into**", ***it refers to*** formation of an infarct, an **area of tissue death**, due to a local lack of oxygen.
- ***Definition***; is the ***irreversible*** **necrosis** (**death** or **damage**) of an area of the heart muscle (myocardium) secondary to prolonged ischemia.



- ***This usually results from*** an **imbalance in oxygen supply and demand**, which is most often ***caused by*** **plaque rupture with thrombus formation** in a coronary vessel, resulting in an ***acute reduction*** of **blood supply** to a portion of the myocardium.
- **Myocardial infarction** is a ***major cause*** of **mortality** and **morbidity worldwide**. Each year, an estimated 785,000 persons will have a new MI in the United States alone, and approximately every minute an American will succumb to one. [Report from the American Heart Association (2012)].
- **MI** ***is considered*** **part of** a spectrum referred to as **acute coronary syndromes** (**ACSs**).

➢ Myocardial Infarction Symptoms:-

- ***The onset of symptoms*** in myocardial infarction (MI) is ***usually*** **gradual, over several minutes** (**30-60 minutes**), and ***rarely*** **instantaneous**.

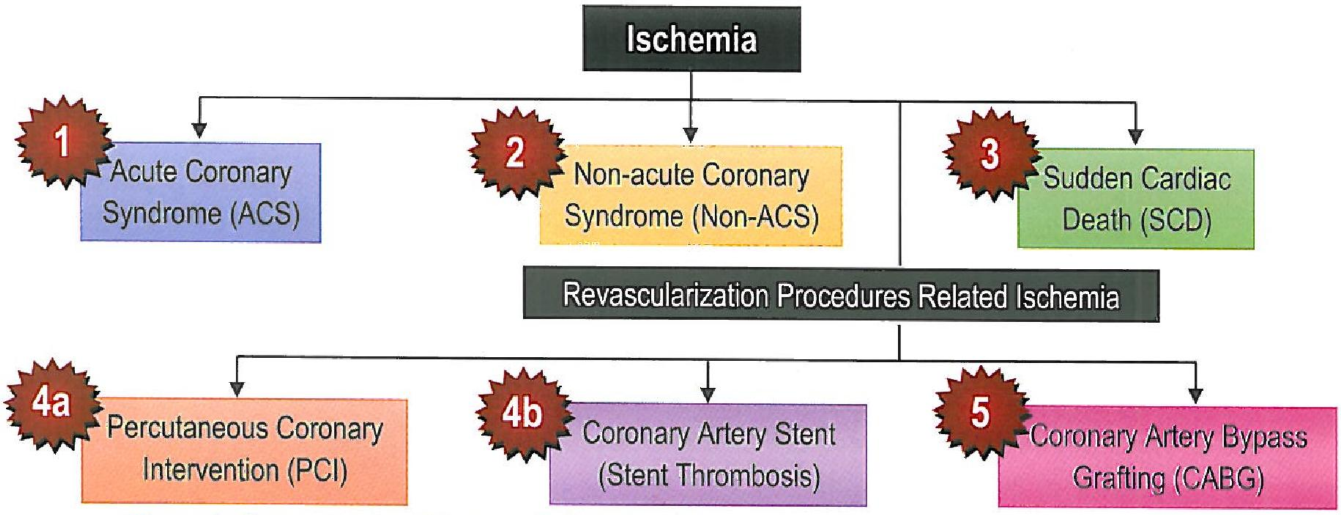


  - **Intense chest pain** that often radiates up to the neck, shoulder, and jaw and down to the ulnar aspect of the left arm.
  - Nausea, indigestion, heartburn or abdominal pain.
  - Shortness of breath (dyspnea) and cold sweat.
  - Fatigue and lightheadedness or sudden dizziness.
- **Chest pain** is ***less common*** **in women**, their most common symptoms are **weakness**, **fatigue** and **dyspnea**.

➢ Myocardial Infarction Risk Factors:-

- **Male Gender**; the incidence of atherosclerotic vascular disease and MI is higher in men than women in all age groups.
- **Age**; men age ≥ 45 and women age ≥ 55 are more likely to have a MI than are younger.
- **Tobacco**; smoking and long-term exposure to second-hand smoke increase the risk of MI.
- **Hypertension**; over time, high BP can cause coronary artery hardness and ↑ risk of MI.
- **Hyperlipidemia**; elevated levels of total cholesterol, LDL, or triglycerides are associated with an increased risk of coronary atherosclerosis and MI.
- **Diabetes Mellitus**; patients with diabetes have a substantially greater risk of atherosclerotic vascular disease in the heart as well as in other vascular beds, and increases the risk of MI.
- **Family History**; a family history of premature coronary disease increases an individual's risk of atherosclerosis and MI.
- **Lack of Physical Activity**; people who get regular aerobic exercise have better cardiovascular fitness, which decreases their overall risk of heart attack.
- **Obesity**; obesity is associated with hyperlipidemia, hypertension and diabetes.
- **Stress**; stress in ways that can increase the risk of a heart attack.

➢ Myocardial Infarction Classification:-

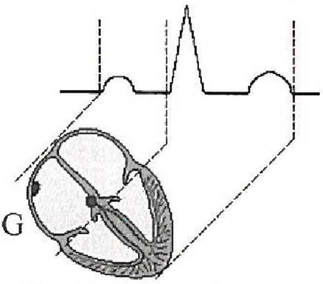

Ischemia
1
Acute Coronary Syndrome (ACS)
2
Non-acute Coronary Syndrome (Non-ACS)
3
Sudden Cardiac Death (SCD)
Revascularization Procedures Related Ischemia
4a
Percutaneous Coronary Intervention (PCI)
4b
Coronary Artery Stent (Stent Thrombosis)
5
Coronary Artery Bypass Grafting (CABG)

- **Type 1**; **Spontaneous Myocardial Infarction**:
  - **MI *related*** to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis.
- **Type 2**; **Myocardial Infarction Secondary to an Ischemic Imbalance**:
  - **MI** where a ***condition other than* CAD** contributes to an imbalance between myocardial oxygen supply and/or demand, e.g. coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy-/brady-cardia, anaemia, respiratory failure, hypotension, and hypertension with or without Left ventricular hypertrophy.
- **Type 3**; **Sudden Cardiac Death Due to Myocardial Infarction**:
  - ***Sudden unexpected cardiac death*** with symptoms suggestive of **myocardial ischemia** and presumed new ischaemic ECG changes or new left bundle branch block (LBBB), but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
- **Types 4 and 5**; ***Myocardial Infarction Associated With Revascularization Procedures***;
  - **Type 4a**; **Myocardial infarction related to percutaneous coronary intervention (PCI).**
  - **Type 4b**; **Myocardial infarction related to stent thrombosis.**
  - **Type 5**; **Myocardial infarction related to coronary artery bypass grafting (CABG).**

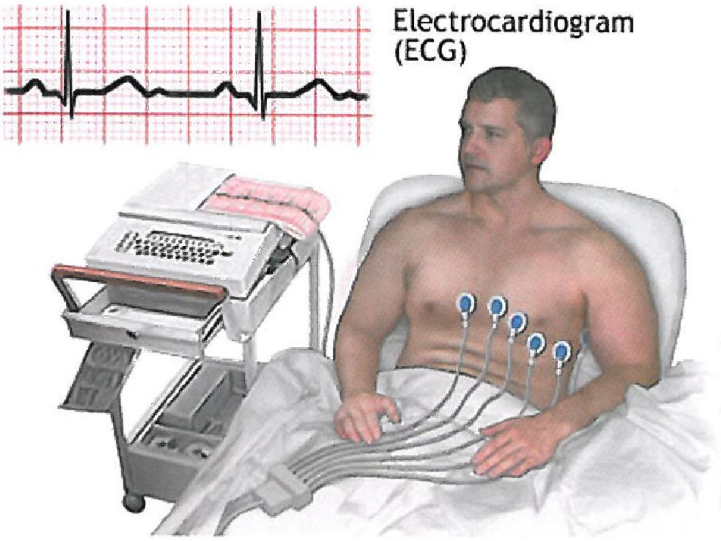
- ***Source***; Third universal definition of myocardial infarction; The European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and the World Heart Federation 2012.

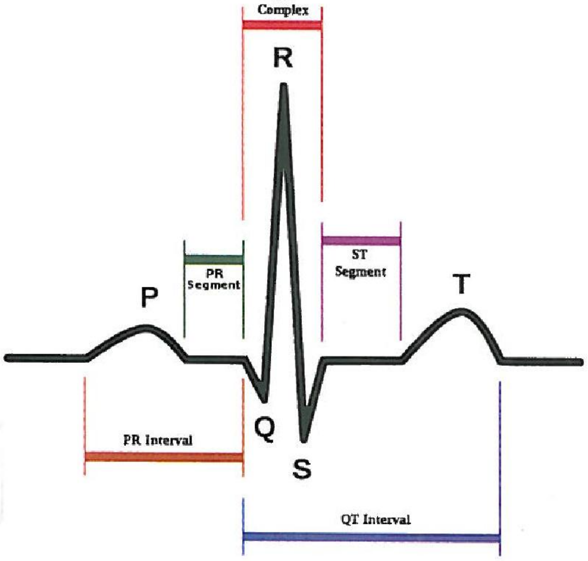
- *Before* diagnosis, **What is the ECG:-**

Electrocardiogram (ECG)



- ECG or EKG (*from the German* Elektrokardiogramm).
- ECG is used to measure the rate and regularity of heartbeats.
- Impulses are recorded as waves displayed on a monitor or printed on paper. In a myocardial infarction, a 12-lead (give more details) ECG can identify if the heart muscle has been damaged in specific areas.
- The ECG is the most important tool in the initial evaluation and triage of patients in whom an acute coronary syndrome. It is confirmatory of the diagnosis in approximately 80% of cases.

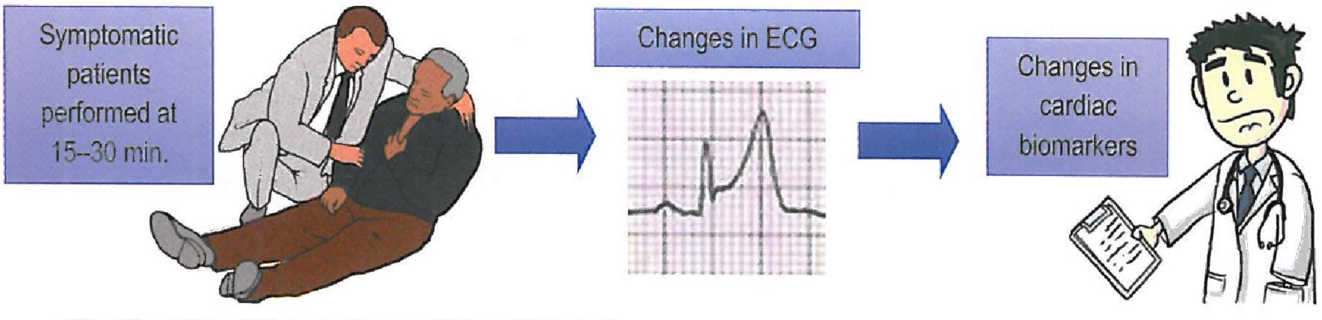

Electrocardiogram
(ECG)


QRS Complex
R
PR Segment
ST Segment
P
T
Q
S
PR Interval
QT Interval

- **Myocardial Infarction Diagnosis:-**

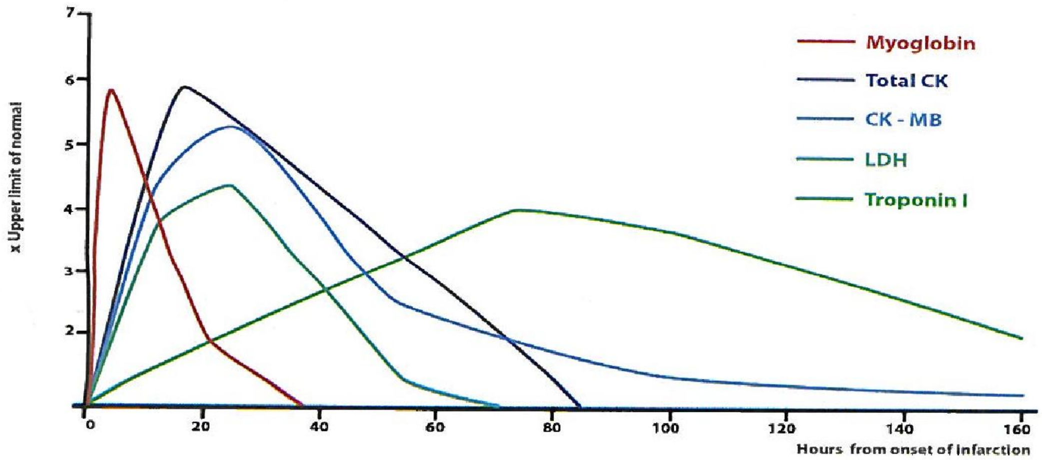
1) Electrocardiogram (ECG);

- **The ECG by itself** is often ***insufficient*** to diagnose acute myocardial ischemia or infarction.
- Patient is diagnosed with MI if two (probable) or three (definite) of the following criteria are satisfied:
    1) Clinical history of ischemic type chest pain lasting for more than 20 minutes.
    2) Changes in serial ECG tracings.
    3) Changes in serum cardiac biomarkers.


Symptomatic patients performed at 15--30 min.
Changes in ECG
Changes in cardiac biomarkers

2) Cardiac Biomarkers (Blood Tests);

- Certain blood tests read as "abnormal" after an MI has occurred because when heart muscle cells die, the chemicals in these cells are released into the blood.
- This does not occur instantly and usually takes several hours.
- These chemicals that released from the heart are called cardiac markers and ***includes***; **creatine phosphokinase (CPK)**, **myocardial creatine kinase (CK-MB)**, **troponins**, **myoglobin** and **lactate dehydrogenase (LDH)**.
- **Troponins (Troponin T & I)** are considered to be ***the best*** and reliance on older tests (such as CK-MB) or myoglobin is discouraged.



Lab Test	After Chest pain	Peak	Duration	Sensitivity and specificity
Troponin T & I	3-6 hours	12-24 hours	5-14 days	The most sensitive and specific test for myocardial damage
CK-MB	3-12 hours	24 hours	48-72 hours	Sensitivity and specificity are not as high as for troponin levels
Myoglobin (Mb)	1-2 hours	4-6 hours	24 hours	Myoglobin has high sensitivity but poor specificity (It may be useful for the early detection of MI)

3) Non-specific Diagnosis;

- **Echocardiography**; uses standard 2-dimensional, 3-dimensional, and Doppler ultrasound to create images of the heart.
- **Computed tomography** (CT) of the chest with intravenous contrast can help exclude pulmonary embolism and aortic dissection.
- **Technetium** (**^{99m}Tc**) **sestamibi** (Cardiolite®) **scan**; is a pharmaceutical agent used in nuclear medicine imaging to visualize areas of reduced blood flow in conjunction with physiological or pharmacological stress.
- Complete blood count, Lipid profile and C-reactive protein and other inflammation markers.

➢ ECG Evolution of Myocardial Infarction:-

1: ***Within Minutes***; Hyper-acute T-wave; more pointer, taller and sharper (Pic. 1).

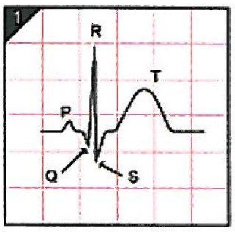
2: ***Within Hours***; Elevation of the ST segment; the hallmark of myocardial infarction (Pic. 2).

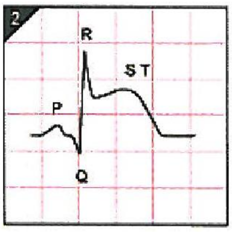
3: ***Within Days***; R wave voltage falls and abnormal Q waves. In addition, T wave inversion and less ST segment elevation (Pic. 3).

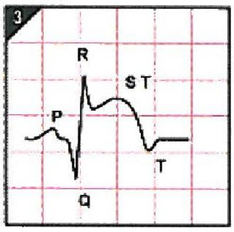
4: ***Within one or more weeks***; The ST segment changes revert to normal. The R wave voltage remains low and the abnormal Q waves persist. Deep, symmetrical T wave inversion may develop at this stage (Pic. 4).

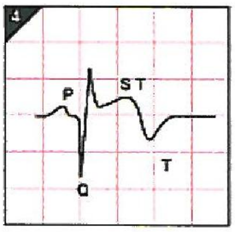
5-6: ***Months after the MI***;

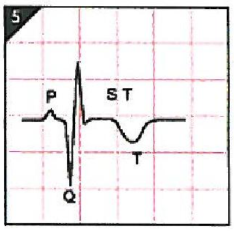
- The abnormal Q waves and reduced R wave voltage persist with T wave inversion (Pic. 5).
- In some cases, after a few months the ECG looks relatively normal (Pic. 6).

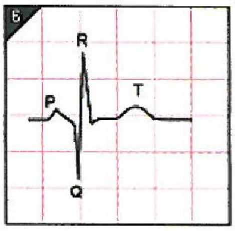












➤ Hospital Management of Acute Coronary Syndromes:-

- *Goals of therapy are* the **immediate relief of ischemia** and the **prevention of MI *and* death**.
- *All patients* should receive **anti-ischemic** and **analgesic medications** early in care; "**MONA**" ***plus*** **β-blocker**;

Morphine

- **Morphine** (***Opioid analgesics***; see page no 380) 1-5 mg IV every 5-30 minutes is reasonable if symptoms are not relieved despite maximally tolerated anti-ischemic medications.

Oxygen

- **Oxygen** if SaO_2 (oxygen saturation) <90%, respiratory distress, or high-risk features of hypoxemia.

Nitroglycerin

- **GTN spray** or **sublingual tablet** (0.3-0.4 mg) every 5 min for up to 3 doses to relieve acute chest pain.
- **GTN IV** 5-10 mcg/minute; titrate to chest pain relief or 200 mcg/minute for persistent ischemia.

Aspirin

- **Aspirin** is the established first-line therapy in all patients with ACS, it reduces the incidence of recurrent MI and death.
- ***A loading dose*** (first hospital day); non-enteric-coated aspirin 162-325 mg is the initial antiplatelet therapy. The subsequent ***maintenance dose*** is 81-162 mg per day.
- **Clopidogrel**; If aspirin allergy or gastrointestinal intolerance, ***loading dose***; 300-600 mg dose is on the **first hospital day**, followed by ***maintenance dose*** of 75 mg daily.

β-blocker

- **β-blocker therapy** is recommended within 12 hours of MI symptoms and is continued indefinitely.
- Treatment with a β-blocker decreases the incidence of ventricular arrhythmias, recurrent ischemia, re-infarction, and, if given early enough, infarct size and short-term mortality.
- Avoid agents with intrinsic sympathomimetic activity; ISA (Acebutolol, Pindolol, Penbutolol).
- **Metoprolol**; 5 mg IV (5 mg slowly over 2 min and repeated twice), then 200 mg/day orally in divided doses.
- **Atenolol**; 10 mg IV (5 mg slowly, repeated once), then 100 mg/day orally.
- **Carvedilol**; 6.25 mg twice daily, titrated to 25 mg twice daily.

- **Other Early Hospital Therapies**;

ACE Inhibitors

- **Oral ACEIs *should be*** used in all patients with left ventricular ejection fraction (LVEF) ≤ 40% and in those with hypertension, diabetes mellitus, or stable chronic kidney disease, without contraindications (hypotension, pregnancy, bilateral renal artery stenosis).
- **ACEIs** should be administered within 24 hours of admission and continued indefinitely.
- **Captopril**; 6.25-12.5 mg orally twice then titrated to 50 mg twice daily (within 24-48 hours).
- **Lisinopril**, 5 mg/day titrated to 10 mg/day, or any of the agents given in pharmacologically equivalent doses.

Aldosterone Antagonists

- **Eplerenone** (see page no. 122) indicated in patients after (post) MI already receiving ACE inhibitor and β-blocker and who have LVEF ≤ 40% and either symptomatic heart failure or diabetes mellitus, without contraindications (Hyperkalemia; potassium ≥ 5.0, creatinine clearance <30 mL/min).

Statins

- **Statin therapy** (see page no. 238) e.g. **Atorvastatin** 40-80 mg/day, **Rosuvastatin** 20-40 mg/day, should be initiated or continued in all patients.

Calcium Channel Blockers

- CCBs are recommended for ischemic symptoms when β-blockers are not successful, are contraindicated, or cause unacceptable side effects.
- Long-acting CCBs and nitrates are recommended for patients with coronary vasospasm.

- ***Simply***; process of blood clot formation;
  1) Platelet activation ⇨ *inhibited by* **Antiplatelet.**
  2) Prothrombin converted to thrombin ⇨ *inhibited by* **Anticoagulant**.
  3) Fibrinogen converted to fibrin by thrombin⇨ *inhibited by* **Thrombolytics (Fibrinolytics)**.

- **Antiplatelet Therapy**; (see page no. 220)

Aspirin

- **Aspirin therapy *is given to* all patients**.
- Aspirin irreversibly inhibit cyclooxygenase (COX) and inhibits the formation of thromboxane A_2 (TXA_2). Within minutes, aspirin prevents additional platelet activation.
- ***A loading dose*** (first hospital day); non-enteric-coated aspirin 162-325 mg is the initial antiplatelet therapy. The subsequent ***maintenance dose*** is 81-162 mg per day.
- *On September 8, 2015*, the U.S. FDA approved Durlaza® (aspirin), the first and only 24-hour, Extended Release Capsules, (162.5mg) for the prevention of stroke and acute cardiac events, including myocardial infarction.

$P2Y_{12}$ Receptor Inhibitors

- **Clopidogrel**, **Prasugrel** and **Ticagrelor**; act by irreversibly inhibit the binding of ADP to its receptors ($P2Y_{12}$ inhibitors) on platelets and, thus, inhibit the activation of the GP IIb/IIIa receptors required for platelets activation.
- **Clopidogrel** used in case of aspirin allergy, ***loading dose***; 300-600 mg once in the **first hospital day**, followed by ***maintenance dose*** of 75 mg daily.
- **Prasugrel**; ***loading dose*** 60 mg ***followed*** by 10 mg daily.
- **Ticagrelor**; ***loading dose*** 180 mg ***followed*** by 90 mg twice daily.
- **Dual Antiplatelet Therapy (DAPT) Dosing Strategies in ACS**;

A) Non-ST-segment elevation MI (NSTEMI);

No stent (No PCI)	- **Aspirin** 162-325 mg once, *followed* by 81-162 mg/day, ***continued PLUS***; a $P2Y_{12}$ inhibitor for up to 12 months; one of: - **Clopidogrel** (Plavix®); 300-600 mg, *followed* by 75 mg/day. ***OR*** - **Prasugrel** (Effient®); 60 mg followed by 10 mg daily. ***OR*** - **Ticagrelor** (Brilinta®); 180 mg followed by 90 mg twice daily.
Bare Metal stent *or* Drug-Eluting Stent or PCI	- **Aspirin** 162-325 mg once, *followed* by 81-325 mg/day, ***continued PLUS***; a $P2Y_{12}$ inhibitor for at least 12 months; one of: - **Clopidogrel** (Plavix®); 300-600 mg, *followed* by 75 mg/day. ***OR*** - **Prasugrel** (Effient®); 60 mg followed by 10 mg daily. ***OR*** - **Ticagrelor** (Brilinta®); 180 mg followed by 90 mg twice daily.

Reference; 2014 American Heart Association/American College of Cardiology (AHA/ACC) guideline for the management of patients with non-ST-elevation acute coronary syndromes.

B) ST-segment elevation MI (STEMI);

No stent (No PCI)	- **Aspirin** 162-325 mg once, *followed* by 81-325 mg/day, ***continued PLUS***; **Clopidogrel** (Plavix®) loading dose of 300 mg then 75 mg daily for at least 14 days and up to 12 months.
Bare Metal stent *or* Drug-Eluting Stent or PCI	- **Aspirin** 162-325 mg once, *followed* by 81-325 mg/day, ***continued PLUS***; a $P2Y_{12}$ inhibitor for 12 months; one of: - **Clopidogrel** (Plavix®); 600 mg, *followed* by 75 mg/day. ***OR*** - **Prasugrel** (Effient®); 60 mg followed by 10 mg daily. ***OR*** - **Ticagrelor** (Brilinta®); 180 mg followed by 90 mg twice daily.

Reference; 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of ST-elevation myocardial infarction.

Glycoprotein IIb/IIIa Inhibitors

- Glycoprotein IIb/IIIa receptors on platelets bind to fibrinogen in the final common pathway of platelet aggregation. Antagonists to glycoprotein IIb/IIIa receptors are potent inhibitors of platelet aggregation.

- GP IIb/IIIa inhibition may be ***beneficial*** in patients with high risk features (e.g. elevated troponin), particularly in those not adequately pretreated with $P2Y_{12}$ inhibition.
- GP IIb/IIIa inhibitors reduce the incidence of composite ischemic events, primarily through a decrease in documented MI, but may increase risk of bleeding.
- All GP IIb/IIIa inhibitor agents should be used in combination with anticoagulant therapy (heparin or bivalirudin) and aspirin.
- ***GP IIb/IIIa Inhibitor Dosing in ACS with or without PCI***;
  - **A) Not Pretreated with $P2Y_{12}$**;
    - **Abciximab** (ReoPro®);
      - **PCI**: 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min. (max 10 mcg/kg) for 12 hours.
      - **ACS without PCI**: Not recommended.
    - **Eptifibatide** (Integrilin®);
      - **PCI**: 180-mcg/kg IV bolus × 2 (10 minutes apart); 2 mcg/kg/minute initiated after first bolus for 18–24 hours.
      - **ACS without PCI**: Of uncertain benefit in patients adequately pretreated with a $P2Y_{12}$ receptor inhibitor; single bolus used as above.
    - **Tirofiban** (Aggrastat®);
      - **PCI**: 25-mcg/kg IV bolus over 3 minutes, then 0.15 mcg/kg/minute for 18–24 hours
      - **ACS without PCI**: 0.4 mcg/kg/minute for 30 minutes (LD infusion), then 0.1 mcg/kg/minute for 18–72 hours.
  - **B) Pretreated with $P2Y_{12}$**;
    - Used if uncertain benefit (not adequately pretreated).

- **Anticoagulant Therapy**; (see page no. 209)

- **Anticoagulants *should be administered to* all patients with ACS *in addition to* antiplatelet therapy** to reduce the risk of intracoronary and catheter thrombus formation.
  - **1) Heparin** is an **injectable anticoagulant**, in nature, heparin is a polymer of ***varying chain size***.
    - A) **Unfractionated heparin** as a heparin that has not been fractionated to sequester the fraction of molecules with low molecular weight.
    - **B) Low-molecular-weight heparin** has undergone fractionation for the purpose of making its pharmacodynamics more predictable, e.g. **Enoxaparin** (Clexane®).
    - Heparins act by enhance the action of anti-thrombin III (AT-III) by causing a conformational change ⇨ activation of AT-III, rapidly combine and inactivate thrombin and Factor Xa (is a activation of Factor X that plays a key role in the blood coagulation cascade).
  - **2) Direct Thrombin Inhibitors (DTIs)**; e.g. **Bivalirudin** (Angiomax®)
  - **3) Direct Factor Xa inhibitors**; e.g. **Fondaparinux** (Arixtra®)
- ***Anticoagulant Dosing in ACS with or without PCI***;
  - **Unfractionated heparin** (Calciparine®);
    - **Loading Dose**; 60 unit/kg IV bolus (max 4000 units).
    - **Maintenance Dose**; 12 units/kg/hour IV (max 1000 units/hour) for 48 hours or end of PCI.
  - **Enoxaparin** (Clexane®);
    - **Loading Dose**; 30 mg IV bolus.
    - **Maintenance Dose**; 1 mg/kg (100 U/kg) SC every 12 hours for 24-48 hours or until end of PCI.
  - **Bivalirudin** (Angiomax®);
    - **Loading Dose**; 0.1 mg/kg IV bolus.
    - **Maintenance Dose**; 0.25 mg/kg per hour, continued until diagnostic angiography or PCI, with only provisional use of GP IIb/IIIa inhibitor.
  - **Fondaparinux** (Arixtra®);
    - 2.5 mg SC daily, continued for the duration of hospitalization or until PCI is performed.
- Anticoagulant therapy is generally discontinued after PCI unless there is a compelling reason to continue.

• Thrombolytic (Fibrinolytic) Therapy; (see page no. 219)

- **Fibrinolytic therapy** is ***indicated for*** **patients with STEMI in which PCI cannot be performed,** ***in absence of*** **contraindication** (includes; history of intracranial hemorrhage, ischemic stroke or closed head injury within the past 3 months, presence of an intracranial malignancy, signs of an aortic dissection, or active bleeding).
- Thrombolytic drugs dissolve blood clots by activating plasminogen, which forms a cleaved product called plasmin. Plasmin is a proteolytic enzyme that is capable of breaking cross-links between fibrin molecules, which provide the structural integrity of blood clots. Because of these actions, thrombolytic drugs are also called "plasminogen activators" and "fibrinolytic drugs".
- ***Fibrinolytic Dosing in ACS***;
    - **Alteplase** (Cathflo Activase®);
        - **≤67 kg**: 15 mg IV Push over 1-2 minutes, then 0.75 mg/kg IV over 30 minutes (maximum 50 mg), then 0.5 mg/kg (maximum 35 mg) over 60 minutes.
        - **>67 kg**: 15 mg IVP over 1-2 minutes, then 50 mg over 30 minutes; then 35 mg over 1 hour (maximum total dose 100 mg).
    - **Reteplase** (Retavase®);
        - 10 units IV; repeat 10 units IV in 30 minutes.
    - **Tenecteplase** (TNKase®);
        - **<60 kg**: 30 mg IV; **60-69 kg**: 35 mg IV; **70-79** kg: 40 mg IV; **80-89 kg**: 45 mg IV.
        - **>90 kg**: 50 mg IV.

• Coronary Artery Revascularization; (see page no. 156)

- **Patients with STEMI** ***should have*** PCI (PCI; consists of diagnostic angiography combined with angioplasty and, usually, stenting) within 90 minutes of arrival at the hospital if skilled cardiac catheterization services are available.
- **Patients with NSTEMI** and high-risk features such as elevated cardiac enzymes, ST-segment depression, recurrent angina, hemodynamic instability, sustained ventricular tachycardia, diabetes, prior PCI, or bypass surgery are recommended to undergo early PCI (<48 hours).
- It is well established that emergency PCI is more effective than fibrinolytic therapy in centers in which PCI can be performed by experienced personnel in a timely fashion.
- PCI can successfully restore coronary blood flow in 90% to 95% of MI patients.

• Aspiration Thrombectomy;

- **Thrombus aspiration** (TA); during this procedure, thrombus is removed by suction.
- ***Indicated*** as **adjunctive therapy during primary PCI** for **STEMI**.

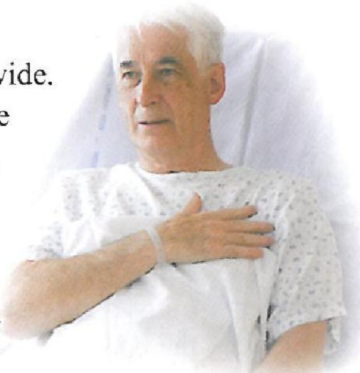
➢ Secondary Prevention After Myocardial Infarction:-

- Most oral medications instituted in the hospital at the time of MI will be continued long term.
- Therapy with aspirin and beta blockade is continued indefinitely in all patients.
- ACE inhibitors are continued indefinitely in patients with congestive heart failure, left ventricular dysfunction, hypertension, or diabetes.
- A lipid-lowering agent, specifically a statin, in addition to diet modification, is continued indefinitely as well.
- Post-MI patients with diabetes should have tight glycemic control according to earlier studies.
- Patient education; Patients should be educated about appropriate cholesterol management, BP, smoking cessation, and lifestyle management (risk factor modification should be addressed in all patients after ACS).

Heart Failure (HF)

➢ Background:-

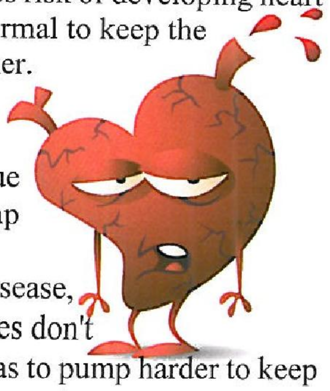
- **Heart Failure** (**HF**) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.
  ***Simply*:** The heart is unable to pump enough blood with each beat.
- **Congestive Heart Failure** (**CHF**); is a type of heart failure, although sometimes the two terms are used interchangeably.
- **Epidemiology**, **Mortality** and **Hospitalizations**;
  - More than 20 million people have heart failure (HF) worldwide.
  - Approximately 5.1 million persons in the United States have clinically manifest HF, and the prevalence continues to rise.
  - In the United States, HF incidence has largely remained stable over the past several decades, with > 650,000 new HF cases diagnosed annually.
  - HF incidence increases with age, rising from approximately 20 per 1,000 individuals 65 to 69 years of age to > 80 per 1,000 individuals among those ≥ 85 years of age.
  - The absolute mortality rates for HF remain approximately 50% within 5 years of diagnosis.
  - In 2013, the total cost of HF care in the United States exceeds $30 billion annually, with over half of these costs spent on hospitalizations.



➢ Terminology:-

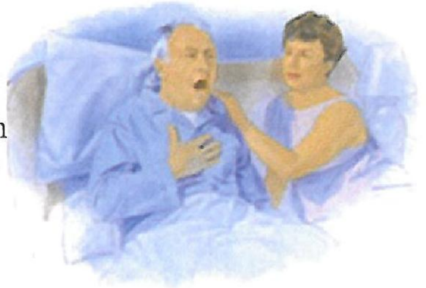
- **Heart Failure** (**HF**); is a physiological state in which cardiac output is insufficient to meet the needs of the body and lungs.
- **Congestive Heart Failure** (**CHF**); is often used as one of the common symptoms is swelling or water retention.
- **Chronic Heart Failure**; is a long term condition, usually kept stable by the treatment of symptoms.
- **Acute Decompensated Heart Failure** (**ADHF**); is a worsening of chronic heart failure symptoms which can result in acute respiratory distress.
- **Ejection fraction** (**EF**)**:** is the fraction of outbound blood pumped from the heart with each heartbeat.
  - It is commonly measured by echocardiogram;
    - **Normal EF; 55-70%** (***means***; 55-70% of the total amount of blood in the left ventricle is pushed out with each heartbeat.).
    - A measurement ***under* 40%** may be evidence of **heart failure**.
  - **Symptoms of EF *under* 40%:**
    - Less blood goes to the brain that may make feel confused.
    - Lungs may fill up with fluid making feel short of breath.
    - Kidneys may not be able to get rid of the fluid.
    - Ankles and feet may swell up.
- **Reduced ejection fraction** (**HF*r*EF**); also referred to as **systolic heart failure**. The heart muscle ***does not contract*** effectively and less oxygen-rich blood is pumped out to the body (**heart failure with ejection fraction *under* 40%**).
- **Preserved ejection fraction** (**HF*p*EF**); also referred to as **diastolic heart failure**. The heart muscle contracts normally but the ventricles ***do not relax*** as they should during ventricular filling (**heart failure with normal ejection fraction**).

➢ Heart Failure Risk Factors:-

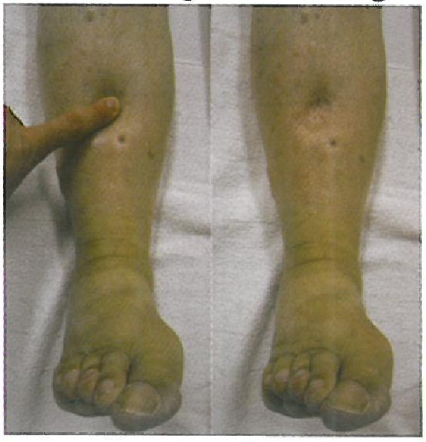


- **High Blood Pressure (Hypertension)**; uncontrolled HBP increases risk of developing heart failure by two to three times, the heart has to pump harder than normal to keep the blood circulating, and over time the chambers get larger and weaker.
- **Coronary Artery Disease**; decreased oxygen supply to the heart muscle, resulting in weakened heart muscle.
- **Past Heart Attack (Myocardial Infarction)**; damaged heart tissue does not contract as well which weakens the heart's ability to pump blood.
- **Abnormal Heart Valves**; heart valve problems can result from disease, infection (endocarditis) or a defect present at birth. When the valves don't open or close completely during each heartbeat, the heart muscle has to pump harder to keep the blood moving. If the workload becomes too great, heart failure results.
- **Heart Muscle Disease** (dilated cardiomyopathy, hypertrophic cardiomyopathy) or inflammation (myocarditis), any damage to the heart muscle, whether because of drug or alcohol use, viral infections or unknown reasons ⇨ increases the risk of heart failure.
- **Congenital Heart Defects**; if the heart and its chambers don't form correctly, the healthy parts have to work harder to make up for it.
- **Lung Disease (Sleep Apnea** = inability to breathe properly during sleep at night); when the lungs don't work properly, the heart has to work harder to get available oxygen to the rest of the body.
- **Diabetes**; increases the risk for developing hypertension and atherosclerosis.
- **Obesity**; can cause the heart to work much harder than for a non-obese person.
- **Other conditions (*less commonly*)**;
  - **Severe Anemia** (low red blood cell count); not enough red blood cells to carry oxygen, the heart tries to move the small number of cells at a faster heart rate. It can become overtaxed from the effort.
  - **Hyperthyroidism** (overactive thyroid gland); this condition causes the body to work at a faster pace, and the heart can be overworked trying to keep up.
  - **Arrhythmia** (abnormal heart rhythm); when the heart beats too fast, too slow or irregularly, it may not be able to pump enough blood to meet all the body's needs.

➢ Heart Failure Symptoms:-



- **Shortness of Breath (Dyspnea)**; breathlessness during activity (most commonly), at rest, or while sleeping, which may come on suddenly. ***Due to***; the blood backs up in the pulmonary veins, return blood from the lungs to the heart, because the heart can't keep up with the supply.
  This causes fluid to leak into the lungs.
- **Persistent Coughing** or **Wheezing**; coughing that produces white or pink blood-tinged mucus. ***Due to***; Fluid builds up in the lungs.

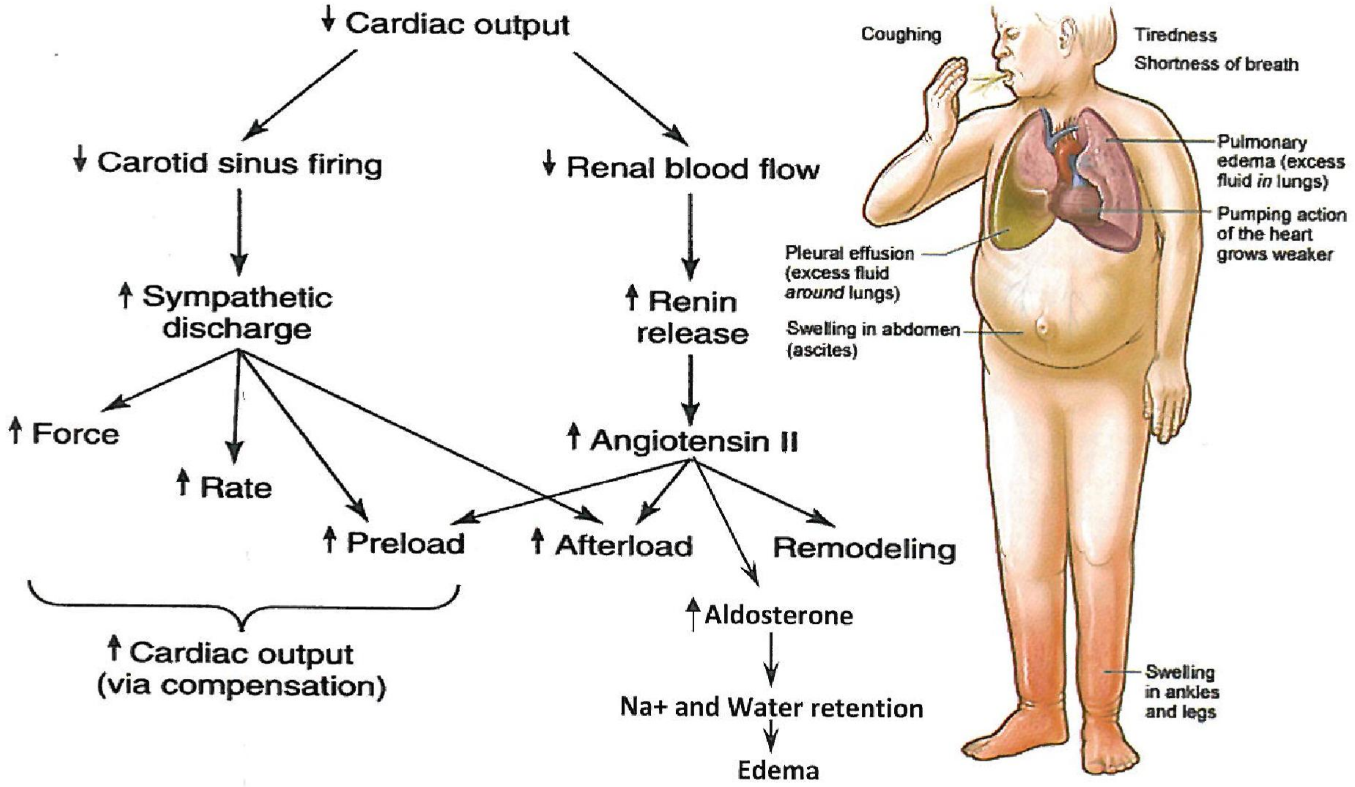


- **Edema (build-up of excess fluid in body tissues)**; swelling in the feet, ankles, legs or abdomen or weight gain (***pitting edema***). ***Due to***; the blood flow out of the heart slows, blood returning to the heart through the veins backs up, causing fluid to build up in the tissues. The kidneys are less able to dispose of sodium and water, also causing fluid retention in the tissues.
- **Tiredness** or **Fatigue**; feeling tired all the time and difficulty with everyday activities, such as shopping, climbing stairs, carrying groceries or walking. ***Due to***; the heart can't pump enough blood to meet the needs of body tissues.

- **Lack of Appetite and Nausea**. ***Due to***; the digestive system receives less blood, causing problems with digestion.
- **Confusion** or **Impaired Thinking**. ***Due to***; changing levels of certain substances in the blood, such as sodium, can cause confusion.
- **Increase heart rate** (**palpitation**). ***Due to***; loss in pumping capacity, the heart beats faster.

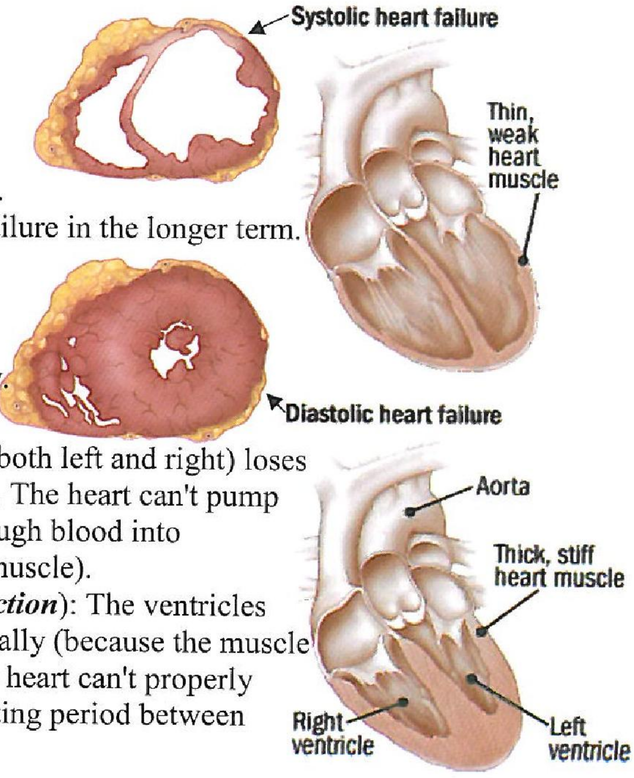
➢ Pathophysiology (Compensatory Mechanisms of Heart Failure):-

- Several natural compensatory mechanisms in heart failure, in an effort to counteract the effect of falling cardiac output on perfusion to vital organs. ***These mechanisms include***:


↓ Cardiac output
↓ Carotid sinus firing
↓ Renal blood flow
↑ Sympathetic discharge
↑ Renin release
↑ Force
↑ Rate
↑ Preload
↑ Afterload
↑ Angiotensin II
Remodeling
↑ Cardiac output (via compensation)
↑ Aldosterone
Na+ and Water retention
Edema
Coughing
Tiredness
Shortness of breath
Pulmonary edema (excess fluid in lungs)
Pumping action of the heart grows weaker
Pleural effusion (excess fluid around lungs)
Swelling in abdomen (ascites)
Swelling in ankles and legs

- Chronic compensatory mechanisms for heart failure include structural alterations in the heart muscle.

➢ Types of Heart Failure:-


Systolic heart failure
Thin, weak heart muscle
Diastolic heart failure
Aorta
Thick, stiff heart muscle
Right ventricle
Left ventricle

- ***According to Structure***;
  - **Left-sided** (**Left Ventricle**) **Heart Failure**;
    - Less pumping by lift ventricle.
    - Less aortic blood flow to the body and brain.
    - Left heart failure often leads to right heart failure in the longer term.
  - **Right-sided** (**Right Ventricle**) **Heart Failure**;
    - Less pumping by right ventricle.
    - Less pulmonary blood flow to the lungs.

* ***Mixed presentations*** (left and right) are commonly.

- ***According to Function***;
  - **Systolic Failure**: The ventricles (usually left or both left and right) loses its ability to contract normally. The heart can't pump with enough force to push enough blood into circulation (**thin**, **weak** heart muscle).
  - **Diastolic Failure**: (also called ***diastolic dysfunction***): The ventricles loses its ability to relax normally (because the muscle has become **thick**, **stiff**). The heart can't properly fill with blood during the resting period between each beat.

Medications

- ***Recently***, there are a **8 classes of drugs** have been shown to be effective in treatment of heart failure.
- ***Depending on*** the **1) severity of HF** or **2) type of HF** and **3) individual patient factors**, one or more of these classes of drugs are administered.
- ***Treatment options of*** acute decompensated heart failure (**ADHF**) ***is different from*** treatment options of chronic heart failure (**CHF**).

		ADHF	CHF
1) Angiotensin-Converting Enzyme (ACE) Inhibitors			✓
2) Angiotensin II Receptor Blockers (ARBs)			✓
3) Angiotensin-Receptor Neprilysin Inhibitors (ARNIs)			✓
4) β-Adrenergic Blocking Agents (β-Blockers)			✓
5) Diuretics	**A) Loop Diuretics**	✓	✓
	B) Thiazide Diuretics	✓	✓
6) Aldosterone Antagonists			✓
7) Vasodilators	**A) Hydralazine + Isosorbide Dinitrate**		✓
	B) Na$^+$ Nitroprusside or IV Nitroglycerin	✓	
	C) Nesiritide	✓	
8) Inotropic Agents	**A) Cardiac Glycosides**		✓
	B) β-Adrenergic Agonists	✓	
	C) Phosphodiesterase III Inhibitors	✓	

- ✓; Drugs which are used.
- ADHF; Acute Decompensated Heart Failure.
- CHF; Chronic Heart Failure.

- First-line therapy for ***people with*** **CHF** ***due to*** **reduced systolic function** (HF*r*EF) should include **angiotensin-converting enzyme** (ACE) **inhibitors** ***or*** **angiotensin receptor blockers** (ARBs) with **β-blockers**.
- ***In*** **acute decompensated heart failure** (ADHF), ***the patient need to*** **hospitalization** to re-establish adequate perfusion and oxygen delivery to end organs.
- ***The major drug classes*** used in **ADHF** include **diuretics** (reducing the fluid level), **inotropes** (improve heart contraction), and **vasodilators** (decrease heart load).

1) Angiotensin-Converting Enzyme (ACE) Inhibitors

- Heart failure leads to activation of the renin-angiotensin-aldosterone system via ***two mechanisms***:
  1) ↑ renin release due to diminished renal perfusion pressure produced by the failing heart.
  2) ↑ renin release by sympathetic stimulation and activation of β receptors in kidney.

- **ACE inhibitors** ***should be prescribed*** to **all patients** ***with*** **HF*r*EF**, unless there is a contraindication.
- **ACE inhibitors** ***benefits***, ***decrease*** **mortality** (25%-50% relative risk reduction compared with placebo), ***decrease*** **hospitalizations** (30%) and improve symptoms.
- **ACE inhibitors** ***mechanism***; ***decrease*** **vascular resistance** (**afterload**) and **venous tone** (**preload**), ***resulting*** in ***increased*** **cardiac output**.
- **ACE inhibitor** ***should be initiated*** at **low doses** (start low and double the dose every 1-4 weeks to target dose).
- ***Monitoring***; renal function and serum K^+ should be assessed within 1-2 weeks of initiation of therapy, recheck at 1, 3 and 6 months, if the function is normal perform it every 6 months.
- ***Avoid use*** in patients who have angioedema or those who are pregnant or plan to become pregnant.
- ***Side effects***; - Angioedema (less than 1%): may switch to ARBs.
  - Cough (20%): may switch to ARBs (less than 1%).
- ***ACE Inhibitors and Recommended Dosing***;

Drug	Initial Dose	Target Dose	Maximum Dose
Captopril	6.25 mg 3 times	50 mg 3 times	50 mg 3 times
Enalapril	2.5 mg twice	10 mg twice	20 mg twice
Fosinopril	5 - 10 mg once	40 mg once	40 mg once
Lisinopril	2.5 - 5 mg once	20 once	40 mg once
Perindopril	2 mg once	8 mg once	16 mg once
Quinapril	5 mg twice	20 mg twice	20 mg twice
Ramipril	1.25 - 2.5 mg once	10 mg once	10 mg once
Trandolapril	1 mg once	4 mg once	4 mg once

- See page no. 101; for a full discussion of ACE inhibitors.

2) Angiotensin II Receptor Blockers (ARBs)

- **ARBs are** ***recommended*** in **patients with HF*r*EF with current or prior symptoms who are unable to take an ACE inhibitor**.
- ARBs are similar to ACE inhibitor which are discussed previously.
- ARBs have the advantage of more complete blockade of angiotensin II action.
- ***ARBs and Recommended Dosing***;

Drug	Initial Dose	Target Dose
Losartan	25 - 50 mg once	150 mg once
Valsartan	20 - 40 mg twice	160 mg twice
Candesartan	4 - 8 mg once	32 mg once

- See page no. 103; for a full discussion of ARBs.

3) Angiotensin-Receptor Neprilysin Inhibitors (ARNIs)

Sacubitril/Valsartan (Entresto®)

- ARNIs are a ***new drug combination*** of a **neprilysin inhibitor** and an **ARB**.
- First approved by FDA in July 7th, 2015.
- Entresto® an oral fixed-dose combination of the ***neprilysin inhibitor*** **Sacubitril** and the ***angiotensin receptor blocker*** (**ARB**) **Valsartan**.
- ***Benefits***; ***reduce*** the risk of death (20%) and hospitalization (21%) in HF patients with HF*r*EF.
- ***Used*** in conjunction with other heart failure therapies, ***in place of*** an ACE inhibitor or other ARBs.
- **Sacubitril** is a pro-drug that is activated to LBQ657, which inhibits neprilysin enzyme.
- **Neprilysin**; is an enzyme that breaks down natural vasoactive peptides (see autacoids chapter page no. 106), including **natriuretic peptides** and **bradykinin**. *Thus*, **Sacubitril** increases the levels of these peptides, ***causing*** **vasodilation** and ***reduction*** of **expands extracellular fluid** (**ECF**) volume via ↑ sodium excretion.
- ***The recommended starting dose*** of Entresto® is 49/51 mg (Sacubitril/Valsartan) twice-daily. Double the dose of Entresto® after 2 to 4 weeks to the target maintenance dose of 97/103 mg (Sacubitril/Valsartan) twice-daily.

4) β-Adrenergic Blocking Agents (β-Blockers)

- Although it may seem counterintuitive to administer drugs with negative inotropic activity in HF.
- β-blockers is attributed, in part, to their ability to prevent the changes that occur because of chronic activation of the sympathetic nervous system.
- These agents decrease heart rate and ***inhibit*** **release of renin** in the kidneys. In addition, **β-blockers** ***prevent*** the **deleterious effects** of **norepinephrine** on the cardiac muscle fibers, ***decreasing*** **remodeling**, **hypertrophy**, and **cell death**.
- **Three β-blockers have been shown to be effective in reducing the risk of death in patients with chronic HF*r*EF**: **Bisoprolol**, **Carvedilol**, and **Metoprolol Succinate** (Long acting).
- **β-blockers** ***should be*** **prescribed** to **all patients *with* HF*r*EF** ***unless*** they have a contraindication to their use or are intolerant of these drugs.
- ***Benefits*** of **β-blockers (when added to an ACE inhibitor)**; ***decrease*** **mortality** (35%), ***decrease*** **hospitalizations** (25%) and ***improve*** **symptoms**.
- ***Should be*** **initiated** at a **very low dose only**, and ***do not*** **discontinue suddenly**.
- ***Dose***; start low and increase (double) the dose every 2 weeks (or slower, if needed) to target dose, aim to achieve target dose in 8-12 weeks
- ***β-blockers and Recommended Dosing;***

Drug	Initial Dose	Target Dose
Bisoprolol	1.25 mg once	10 mg once
Carvedilol	3.125 mg twice	25 mg twice
Carvedilol CR	10 mg once	80 mg once
Metoprolol Succinate (CR/XL)	12.5 to 25 mg once	200 mg once

- See page no. 79; for a full discussion of β-blockers.

- May, 2016; The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) recently updated and added two new drugs to heart failure guidelines: sacubitril/valsartan (Entresto®) and ivabradine (Procoralan®).

5) Diuretic Agents

- **Diuretics** are *recommended* in **patients *with* HF*r*EF *who have evidence of*** **fluid retention**, unless contraindicated, **to improve symptoms** (*relieve* **pulmonary congestion** and **peripheral edema**).
- **Diuretics** ***decrease*** **plasma volume**, subsequently, ***decrease*** **preload and afterload.**
- **Loop diuretics** are ***preferred*** diuretic agents for use in most patients with HF.
- **Thiazide diuretics** may be ***considered*** in **hypertensive patients *with* HF *and* mild fluid retention.**
- **Diuretics** ***should be*** prescribed to **all patients *with* fluid retention.**
- **Diuretics** ***should be*** ***combined with*** an **ACE inhibitor, β-blocker** and **aldosterone antagonist.**
- ***Long-term*** (months to years): ***No benefit*** on **mortality**.
- **Once fluid retention has resolved**, treatment with the diuretic ***should be*** **maintained** in some patients ***to prevent*** the **recurrence of volume overload.**
- ***Dose***; ***start with*** a **low initial dose**; titrate according to the patient's weight and diuresis.
- ***Monitoring***: serum K and Mg as needed, especially with loop diuretics.
- ***Diuretics and Recommended Dosing;***

Loop Diuretics	Initial Daily Dose	Thiazide Diuretics	Initial Daily Dose
Furosemide	20 - 40 mg once or twice	**Hydrochlorothiazide**	25 mg once or twice
Bumetanide	0.5 - 1 mg once or twice	**Chlorthalidone**	12.5 - 25.0 mg once
Torsemide	10 - 20 mg once		

- Furosemide is the most commonly used diuretic in HF.
- ***For ADHF;***
  - Diuretics considered first-line therapy for management of ADHF associated with fluid overload.
  - ***Most commonly used***; furosemide 40 mg orally = furosemide 20 mg IV = bumetanide 1 mg IV or orally = torsemide 20 mg IV or orally.

See page no. 119 for a full discussion of diuretics.

6) Aldosterone Antagonists

- In addition to sodium and water retention, aldosterone has been shown to cause coronary inflammation, cardiac hypertrophy, myocardial fibrosis and ventricular arrhythmias.
- **Spironolactone** is a nonselective aldosterone antagonist, **Eplerenone** is selective antagonist.
- **Eplerenone** has a lower incidence of endocrine-related side effects than **Spironolactone**, due to its reduced affinity for glucocorticoid, androgen and progesterone receptors.
- **Aldosterone antagonists** are ***recommended in patients with***;
  - **Patients with NYHA class II-IV HF and who have LVEF of 35% or less.**
  - **Patients with HF*r*EF after myocardial infarction.**
- ***Benefits***;
  - **Spironolactone** in **NYHA class III-IV HF**; decrease mortality (30%), decrease hospitalizations for HF (35%) and improve symptoms.
  - **Eplerenone** in **NYHA class II HF**; decrease mortality (24%), decrease hospitalizations for HF (42%) and improve symptoms.
  - **Eplerenone** in **LV dysfunction after MI**; decrease mortality (15%), decrease hospitalizations for HF (14%) and improve symptoms.
- **Aldosterone antagonist** ***should be added*** to ACE inhibitor (or ARB) and β-blocker therapy.
- ***Monitoring***: **K^+ levels** and **renal function** ***should be*** rechecked within 2 to 3 days and again at 7 days after initiation of an aldosterone receptor antagonist to minimize the risk of life-threatening hyperkalemia (serum creatinine should be less than 2.5 mg/dL for men and less than 2.0 mg/dL in women, and K^+ should be less than 5.0 mEq/L).
- ***Dosing of Aldosterone Antagonists;***

Drug	Initial Dose	Target Dose
Spironolactone	12.5 - 25 mg once	25 mg once or twice
Eplerenone	25 mg once	50 mg once

- See page no. 122; for a full discussion of aldosterone antagonists.

7) Vasodilators

A) Hydralazine + Isosorbide Dinitrate *(only for ADHF)*

- **Isosorbide Dinitrate (ISDN)** are commonly used venous dilators to ***reduce*** **preload.**
- **Hydralazine** reduce systemic arteriolar resistance and ***decrease*** **afterload.**

* **The combination** of **Hydralazine** and **Isosorbide Dinitrate** (BiDil®) are ***recommended in addition to* ACE inhibitors + β-blockers to reduce morbidity and mortality for patients self-described as African Americans with HF*r*EF.**

* **The combination** of **Hydralazine** and **Isosorbide Dinitrate** (BiDil®); ***may be useful*** in **patients with current or prior symptoms of HFrEF who are unable to tolerate an ACEI or an ARB.**

- ***Benefits***; decrease mortality (43%), decrease hospitalizations for HF (39%) and improve symptoms.
- ***Dosing and administration;***

Initial Dose	Target Dose
37.5 mg hydralazine + 20 mg ISDN 3 times daily	75 mg hydralazine + 40 mg ISDN 3 times daily

B) Na^+ Nitroprusside or IV Nitroglycerin *(only for ADHF)*

- **Sodium Nitroprusside** (Nipride®); is a powerful short acting parenterally vasodilator. It is dilates both arterial and venous vessels, ***reductions*** in **preload, afterload, arterial BP** and ***relief*** **pulmonary congestion** make it particularly ***useful for*** **patients with ADHF and advanced HF.** ***Typical dose***; 0.5-1 mcg/kg/minute IV.
- **IV Nitroglycerin**; is a rapid and short acting organic nitrate, it produces venous vasodilation ***reductions*** in **preload, arterial BP** and ***relief*** **pulmonary congestion** make it particularly ***useful for*** **patients with ADHF.** ***Typical dose***; 25-75 mcg/minute IV, titrated to response.

C) Nesiritide *(only for ADHF)*

- **Nesiritide** [ness-EAR-a-tide] (Natrecor®); is a recombinant human brain-type natriuretic peptide (BNP), ***act by*** binds to **natriuretic peptide receptor A** to stimulate guanylate cyclase and production of cGMP ⇨ vasodilatation, and it has a natriuretic effects.
- BNP is an endogenous hormone produced in the ventricular myocardium in response to increased wall stress, hypertrophy, and volume overload (see page no. 106).
- ***Used in*** **patients with ADHF who have dyspnea at rest or with minimal physical activity.**
- ***Typical dose***; 0.01 mcg/kg/minute IV, May omit bolus if low systolic blood pressure.
- See page no. 132 for a full discussion of vasodilators.

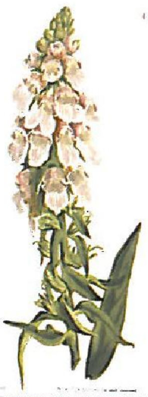
- The FDA has approved Ivabradine (Procoralan®) to reduce the risk of hospitalization for worsening heart failure (HF) in patients with stable, symptomatic chronic HF with left ventricular ejection fraction (LVEF) ≤35% who are in sinus rhythm with a resting heart rate (HR) ≥70 beats per minute (bpm) and either are on maximally tolerated doses of β-blockers or have a contraindication to beta-blocker use (See page 155 for more details).

8) Inotropic Agents

A) Cardiac Glycosides

Digoxin (Lanoxin®)	**Digitoxin** (Unidigin®)	**Ouabain** (Uabanin®)

- **Cardiac glycosides** are a family of compounds that are derived from the foxglove plant (***Digitalis purpurea***).
- **Cardiac glycosides** are **organic compounds *containing*** a glycoside often called **digitalis** or **digitalis glycosides.**
- The therapeutic benefits of digitalis were first described in 1785.
- Cardiac glycosides act on the contractile force of the cardiac muscle. *Because* of their potency in disrupting the function of the heart, **most are extremely toxic**.
- The ***most widely used agent*** is **Digoxin** [di-JOX-in].
- **Digitoxin** [dij-i-TOK-sin] is ***seldom used*** due to its considerable duration of action.
- **Ouabain** [OH-BA-in] is a cardiac glycoside, but is ***very rarely clinically used*** and obtained from ***Strophanthus gratus***. It is commonly used in cell biological studies.



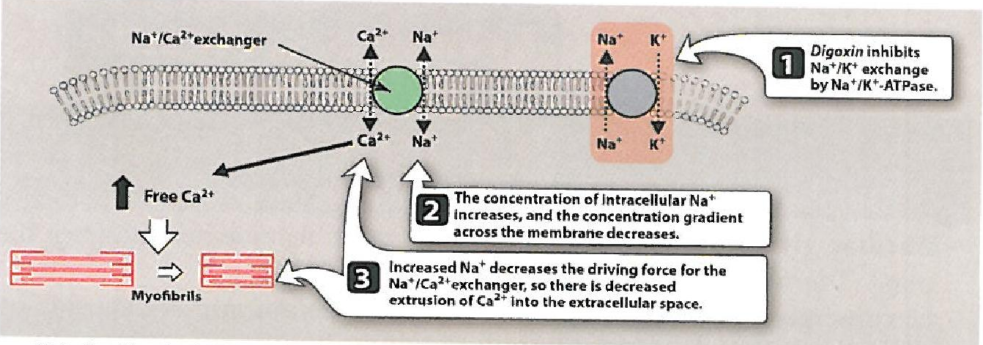
Pharmaco Kinetics

		Digoxin	Digitoxin	Ouabain
Routes of administration		Oral & IV	Oral only	IV only
Oral bioavailability		75%	90-100%	0%
Half-life ($T_{1/2}$)		36 hours (1.5 days)	7 days	21 hours
Lipid solubility		Moderate	High	Less
Plasma protein binding		25%	95%	0%
Potency		Moderate	High	Less
Elimination		Kidneys	Liver	Kidneys
Excretion		Urine only	Urine and feces	Urine only
Kidney dysfunction		Not safe	Safe	Not safe
Liver dysfunction		Safe	Not safe	Safe
Plasma Levels	Normal	0.5 - 2 ng/ml	10 - 40 ng/ml	-
	Recommended	0.5 - 0.9 ng/mL	-	-
	Toxic	> 2 ng/mL	> 45 ng/mL	-
Therapeutic index		Extremely Low	Extremely Low	Extremely Low

Pharmaco dynamics

- ***Effects on the heart***:
  - **+ve inotropic effect** (***increase* force of contraction**) by direct effect on the heart.
  - **-ve chronotropic effect** (***decrease* heart rate**) by direct effect and vagal effect (unclear mechanism).
  - **-ve dromotropic effect** (***reduces*** conduction velocity of electrical impulses through the AV node).
  - ***Increase* cardiac output** and ***increase* cardiac efficiency**.
  - ***Decrease* blood volume** (diuresis due to ↑ CO) in CHF only.
  - **Finally *it cause*; Short Strong Systole *with* Long Diastole.**
- ***Other effects***:
  - ***Kidney***; **diuretic effects *only* in CHF patients** (***due*** to it ↑ CO ⇨ ↑ renal blood flow and ↓ renin release ⇨ ↓ aldosterone release ⇨ ↑ Na^+ and water excretion.
  - ***CNS effects***; Stimulation of the vagal center and chemoreceptor trigger zone (CTZ) results in nausea, vomiting, diarrhea & anorexia. ***Other CNS effects*** include blurred vision, headache, dizziness, fatigue, and hallucinations.
  - ***Endocrine effects***; Gynecomastia in male (rare) due to ability to bind to estrogen receptor (steroid similarity structure).

Mechanism OF Action

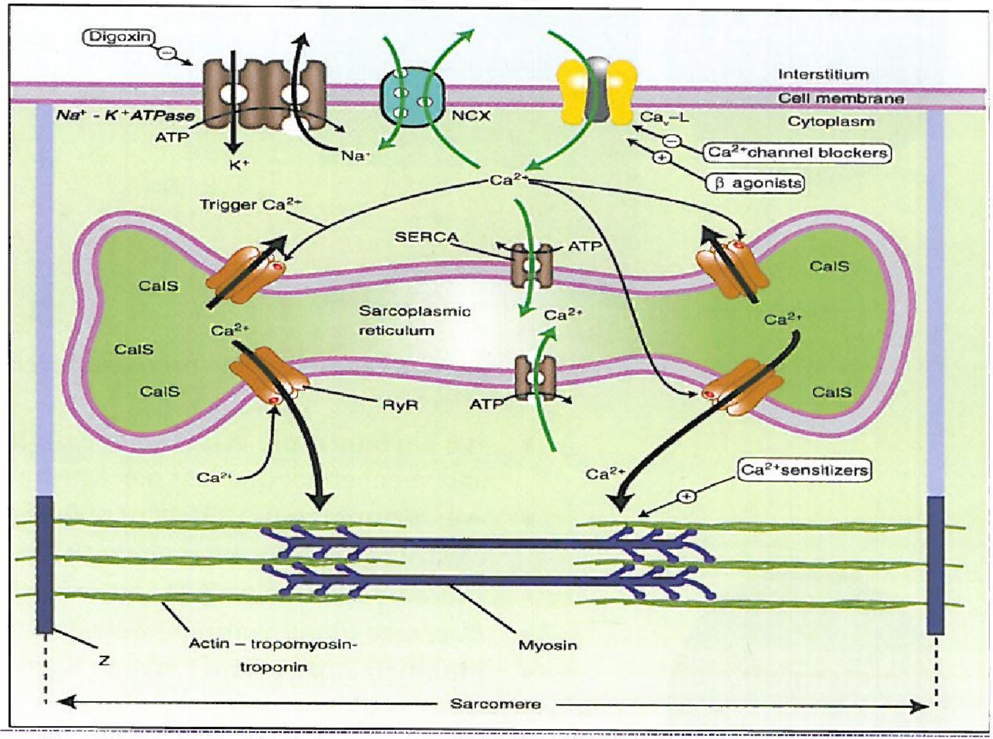

Na⁺/Ca²⁺exchanger
Ca²⁺
Na⁺
Na⁺
K⁺
Ca²⁺
Na⁺
Na⁺
K⁺
Free Ca²⁺
Myofibrils
1
2
3

Digoxin inhibits Na^+/K^+ exchange by Na^+/K^+-ATPase.

The concentration of intracellular Na^+ increases, and the concentration gradient across the membrane decreases.

Increased Na^+ decreases the driving force for the Na^+/Ca^{2+}exchanger, so there is decreased extrusion of Ca^{2+} into the extracellular space.

- **Digitalis *inhibits* Na^+/K^+ ATPase** (adenosine triphosphatase) **enzyme** *lead to*, ***inhibits* Na^+/K^+ exchange**, *causes* ⇨ ***increase* intracellular Na^+.**
- ***Increase* intracellular Na^+**, leads to ⇨ ***accumulation* of intracellular calcium** *via the* **Na^+-Ca^{2+} exchange system.**
- ***In the heart*, increased intracellular calcium *causes* more calcium to be released by the sarcoplasmic reticulum**, thereby making more calcium available to bind to troponin-C, which increases contractility (+ve inotropic effect).
- **Digitalis** also ***increase* vagal efferent activity** to the heart (**parasympathomimetic action**) ⇨ ***decreases* heart rate** (-ve chronotropic effect) and ***reduces* conduction velocity** through the AV node (-ve dromotropic effect), **making it useful for atrial fibrillation.**


Digoxin
Na⁺ - K⁺ATPase
ATP
K⁺
Na⁺
NCX
Cav–L
Interstitium
Cell membrane
Cytoplasm
Ca²⁺channel blockers
β agonists
Ca²⁺
Trigger Ca²⁺
SERCA
ATP
CalS
CalS
CalS
CalS
CalS
CalS
Sarcoplasmic reticulum
Ca²⁺
Ca²⁺
Ca²⁺
RyR
ATP
Ca²⁺
Ca²⁺
Ca²⁺sensitizers
Actin – tropomyosin-troponin
Myosin
Z
Sarcomere

Therapeutic Uses

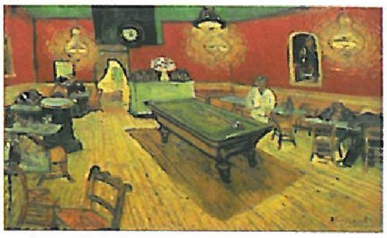
- ***In a long-term trial***, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization.
- **Digoxin therapy** is ***indicated*** in **patients with severe HFrEF after initiation of ACE inhibitor, β-blocker** and **diuretic therapy**.
- ***Better results*** are obtained in **patients with atrial fibrillation or flutter.**
- **Patients with mild to moderate HF** often respond to treatment with ACE inhibitors, β-blockers, aldosterone antagonists, direct vasodilators, and diuretics and ***may not require* digoxin.**
- ***Benefits***; (a) Improved symptoms. (b) Improved exercise tolerance. (c) Decreased hospitalizations. (d) No effect on mortality.

Dose

- **Digoxin**;
  - **Therapy with digoxin** (digitalization) is commonly ***initiated and maintained*** at a dose of **0.125 to 0.25 mg daily**.
  - **Low doses (0.125 mg daily or every other day)** should be used initially if the patient is **>70 years of age**, has **impaired renal function**, or has a **low lean body mass**.
  - **Higher doses** (0.375 to 0.50 mg daily) are rarely used or needed in the management of patients with HF.
- **Monitoring Serum Digoxin Concentration** (**SDC**);
  - Doses of digoxin that achieve a plasma concentration of drug in the range of 0.5 to 0.9 ng/mL.
  - **Most heart failure patients** achieve a serum concentration of 0.5 to 1.0 ng/mL ***with doses*** of 0.125 to 0.25 mg/d.
  - Serum digoxin concentrations (SDC) should be monitored to guide therapy in patients at high risk for developing digoxin intoxication.
  - An SDC should be obtained ≈14 to 21 days after therapy initiation.
  - The half-life of digoxin is ≈ 2 days in patients with normal renal function and is prolonged to 4-7 days in patients with renal failure.
  - Sampling for digoxin concentrations should be performed no sooner than 8 hours after the last dose.

Toxicity

- ***The major* side effect** of digitalis compounds is **cardiac arrhythmia**.
- **Digitalis toxicity** is one of the most common adverse drug reactions leading to hospitalization.
- ***Early manifestation of toxicity***;
  - **Anorexia**, **nausea**, and **vomiting**.
  - **Bradycardia**.
- ***Late manifestation of toxicity***;
  - ***Eye***; Visual disturbance and coloured vision ***called*** **Chromatopsia** or **Xanthopsia** (A form of chromatopsia); is a color vision deficiency in which there is a predominance of yellow in vision.



  - ***CVS***; Arrhythmias; premature ventricular depolarizations (50%), AV nodal arrhythmias (50%), AV conduction disturbances (36%).
  - ***GIT*** (25%); Anorexia, nausea, vomiting and diarrhea (NVD).
  - ***CNS*** (25%); Hallucination, convulsions, confusion and delusions.
  - ***Endocrine***; Gynecomastia (rare).
- ***Factors that increase digitalis toxicity***;
  - Drugs increase toxicity e.g. thiazide and loop diuretic (hypokalemia).
  - Organ dysfunction e.g. Kidneys (Digoxin) and liver (Digitoxin).
  - Dosing errors.
  - Old age (>70 years of age).
  - Serum electrolytes disturbances: hypokalemia, hypomagnesaemia or hypercalcemia.

- Broad-spectrum antibiotics such as erythromycin can increase the oral bioavailability of digoxin because they kill bacteria present in normal intestinal flora (mainly *Eubacterium lentum*) that are able to metabolize digoxin.

➢ Treatments of Digitalis Toxicity:-

Digoxin Immune Fab (Ovine) (Digibind®)

- **Digoxin Immune Fab (Ovine)**, is a sterile lyophilized powder of antigen binding fragments (Fab) ***derived from*** specific **antidigoxin antibodies** raised in sheep.
- **Digibind *binds* molecules of digoxin**, making them unavailable for binding at their site of action on cells in the body.
- **Digoxin Immune Fab** (Ovine), is ***indicated for*** **treatment of potentially life-threatening digoxin intoxication**.

Dose

- The dose depends on the serum digoxin concentration and the weight of the patient.

A) Skin Testing; Skin testing may be appropriate for high risk individuals.

1: Diluting 0.1 mL of reconstituted Digibind (9.5 mg/mL) in 9.9 mL sterile isotonic saline (1:100 dilution, 95 µg/mL).

2: Injecting 0.1 mL of the 1:100 dilution (9.5 µg) intradermally and observing for an urticarial wheal surrounded by a zone of erythema. The test should be read at 20 minutes.

B) Dose Calculations;

1: Calculation of body load of digitalis;

For digoxin

$$\text{Body load in mg} = \frac{(\text{SDC})(5)(\text{weight in kg})}{1000}$$

- Serum digoxin conc. (SDC) in ng/mL.
- Volume of distribution of digoxin in the body (5 L/kg).

For digitoxin

$$\text{Body load in mg} = \frac{(\text{SDC})(0.5)(\text{weight in kg})}{1000}$$

- Serum digoxin conc. (SDC) in ng/mL.
- Volume of distribution of digoxin in the body (0.5 L/kg).

2: Calculation of dose (number of Digibind® vials);

- Each vial of Digibind® contains 38 mg of purified digoxin-specific Fab fragments which will bind approximately 0.5 mg of Digoxin (or Digitoxin).

$$\text{Dose (in \# of vials)} = \frac{\text{Body Load (mg)}}{0.5(\text{mg / vial})}$$

TABLE : Adult Dose Estimate of DIGIBIND (in # of vials) from Steady-State Serum Digoxin Concentration

	Serum Digoxin Concentration (ng/mL)						
Patient Weight (kg)	**1**	**2**	**4**	**8**	**12**	**16**	**20**
40	0.5 v	1 v	2 v	3 v	5 v	7 v	8 v
60	0.5 v	1 v	3 v	5 v	7 v	10 v	12 v
70	1 v	2 v	3 v	6 v	9 v	11 v	14 v
80	1 v	2 v	3 v	7 v	10 v	13 v	16 v
100	1 v	2 v	4 v	8 v	12 v	16 v	20 v

v = vials

B) β-Adrenergic Agonists *(only for ADHF)*

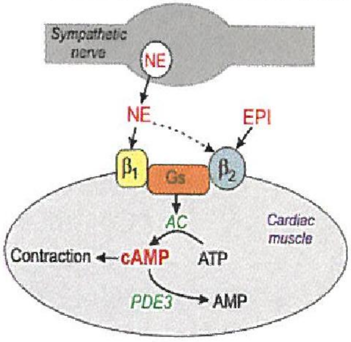
Dopamine (Intropin®) | **Dobutamine** (Dobutrex®)

- **Dopamine**; is a cardiac stimulant drug (β_1 agonist effect) ⇨ +ve inotropic. It has renal blood vessels dilatation effect (D_1 agonist effect) ⇨ increase blood flow to the kidneys).
- **Dobutamine** is a ***predominantly*** β_1 receptor agonist ⇨ improve cardiac performance by causing positive inotropic effects with slight peripheral vasodilation.
- **Dobutamine** is ***the most commonly used*** **inotropic agent.** ***Typical dose***; 5 mcg/kg/minute IV.
- ***Both drugs*** must be given by IV infusion and are primarily ***used in*** the **short-term treatment of ADHF** in the hospital setting.
- See page no. 62 for a full discussion of β-Adrenergic Agonists.

C) Phosphodiesterase III Inhibitors *(only for ADHF)*

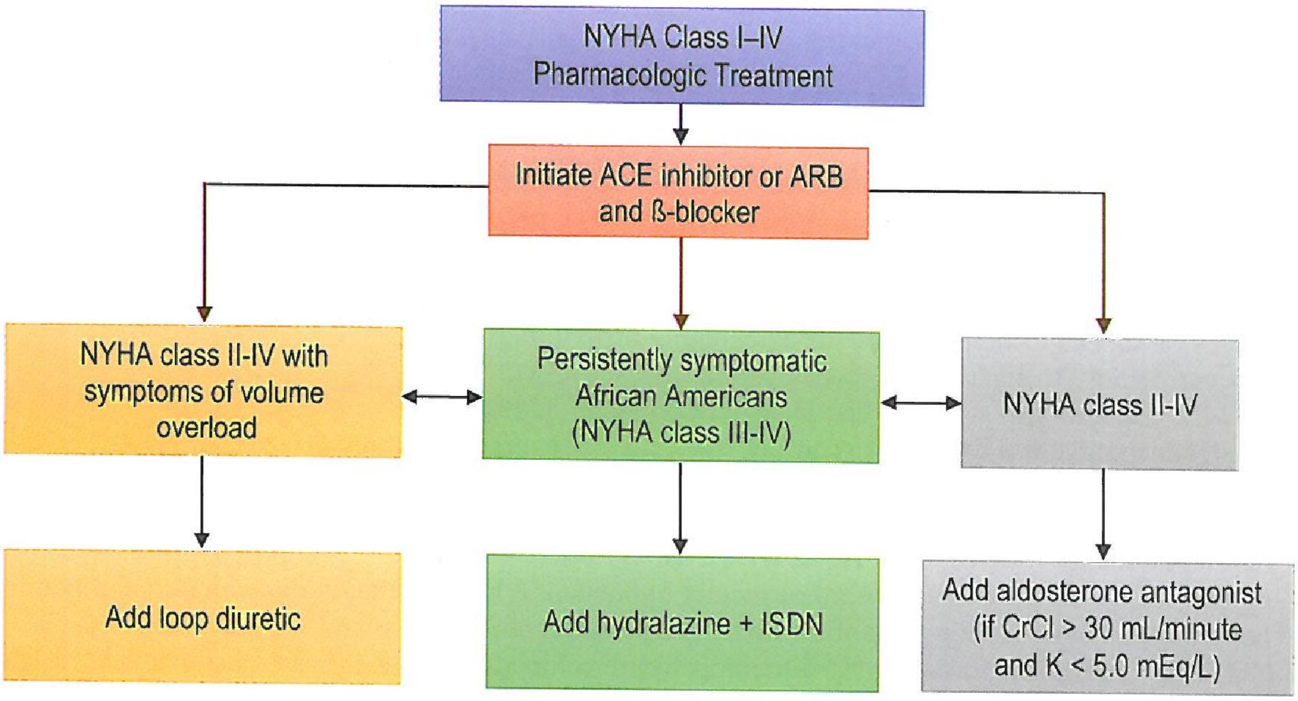
Amrinone (Inocor®) | **Milrinone** (Primacor®)

- **Amrinone** [AM-ri-none] and **Milrinone** [MILL-ri-none] are a phosphodiesterase (PDE) 3 inhibitor.
- ***Mechanism of Action***;
  - PDE III is present in cardiac muscle and vascular smooth.
  - PDE III responsible for degrades cAMP.
  - Inhibition of PDE III, cAMP cannot be inactivated ⇨ accumulation of cAMP.
  - ↑ cAMP in ***cardiac muscle*** ⇨ increase Ca^{2+} influx ⇨ contraction of the heart ⇨ **+ve inotropic effect**.
  - ↑ cAMP in ***vascular smooth muscle*** ⇨ relaxes both arterial & venous smooth muscle ⇨ **reducing both preload and afterload**.


Sympathetic nerve
NE
NE
EPI
β1
Gs
β2
AC
Cardiac muscle
Contraction
cAMP
ATP
PDE3
AMP

- ***Both drugs*** must be given by IV and are primarily ***used in*** the **short-term treatment of ADHF** in the hospital setting.
- ***Dose***;
  - **Amrinone**; 0.75 mg/kg IV bolus over 2-3 minutes, then 5-10 mcg/kg/min IV.
  - **Milrinone**; 50mcg/kg IV bolus, then 0.375 mcg/kg/min IV.
- ***Side effects***; Arrhythmia, Hypotension and Thrombocytopenia.

➢ Algorithm for Pharmacologic Management of HF*r*EF:-


NYHA Class I–IV
Pharmacologic Treatment
Initiate ACE inhibitor or ARB and ß-blocker
NYHA class II-IV with symptoms of volume overload
Persistently symptomatic African Americans (NYHA class III-IV)
NYHA class II-IV
Add loop diuretic
Add hydralazine + ISDN
Add aldosterone antagonist (if CrCl > 30 mL/minute and K < 5.0 mEq/L)

➢ Drugs to avoid or use with caution in HF*r*EF:-

- **Non-steroidal anti-inflammatory drugs** (NSAIDs, including selective cyclooxygenase-2 inhibitors); promote Na^+ and water retention, blunt diuretic response and increase morbidity and mortality.
- **Corticosteroids**: promote Na^+ and water retention.
- **Class I and III antiarrhythmic agents**; (***except for*** Amiodarone and Dofetilide); -ve inotropic activity, pro-arrhythmic effects.
- **Calcium channel blockers (CCBs)** (except for Amlodipine and Felodipine); -ve inotropic activity and neurohormonal activation.
- **Minoxidil**; fluid retention and neurohormonal activation.
- **Thiazolidinediones**: fluid retention.
- **Metformin**; increased risk of lactic acidosis.
- **Amphetamines**; α- and β-agonist activity and tachycardia.
- **Nutritional supplements**.
- **Hormonal therapies**.
- **Itraconazole**: -ve inotropic activity.
- **Pregabalin**; inhibition of calcium channels.

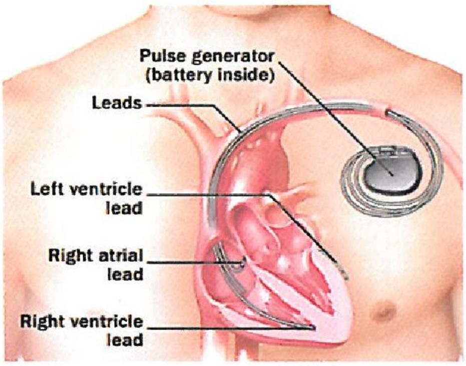
➢ Management of HF*p*EF or Diastolic Dysfunction:-

- **General treatment goals of diastolic dysfunction**;
  - Control hypertension, control tachycardia and reduce preload.
  - Aggressively investigate, repair and treat myocardial ischemia.
- **Pharmacologic therapy for diastolic dysfunction**;
  - **ACE inhibitors** or **ARBs**; reduce hospitalizations and treat hypertension.
  - **β-blockers**, **verapamil** and **diltiazem**: benefits are targeted symptom relief.
  - **Digoxin**; no effect on all-cause mortality or on all-cause CV hospitalizations.

Novel Drug in Clinical Development for Heart Failure

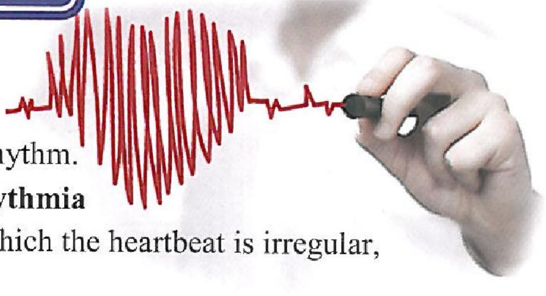
- Vasopeptidase inhibitors (e.g. Omapatrilat, Sampatrilat and Fasidotrilat) are a new class of cardiovascular agents capable of inhibiting neutral endopeptidase and angiotensin-converting enzymes, which leads to potentiation of natriuretic peptide actions and suppression of the renin-angiotensin system.
- Ularitide and Carperitide which are ANP (atrial natriuretic peptide) analogues.

Device Therapy



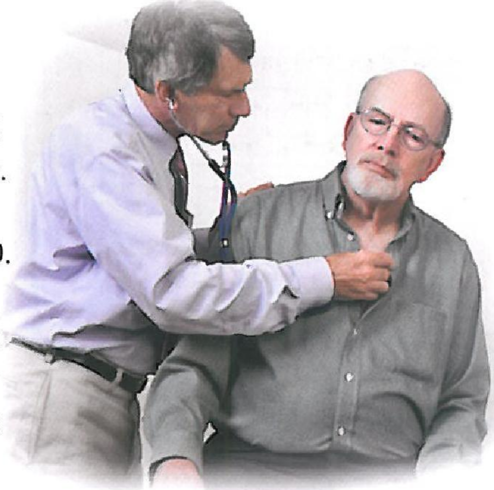
- **Implantable Cardioverter Defibrillator (ICD)** and **Cardiac Resynchronization Therapy (CRT)**; is a small device that's placed in the chest or abdomen. Act by generation of electrical pulses or shocks to help control life-threatening arrhythmias, especially those that can cause sudden cardiac arrest (SCA).
- ICD have one or two wires, called leads, CRT system adds a third, attaching a lead to the left ventricle.
- ICD: recommended for primary prevention of sudden cardiac death.
- **Left Ventricular Assist Device (LVAD)** is a battery-operated, mechanical pump-type device that's surgically implanted. It helps maintain the pumping ability of a heart that can't effectively work on its own.
- **CORolla® Implant**; CorAssist (Israeli company) developed the CORolla, an elastic device that is implanted inside the left ventricle of the heart by a minimally invasive procedure on a beating heart used for diastolic heart failure.

Arrhythmias



➢ Background:-

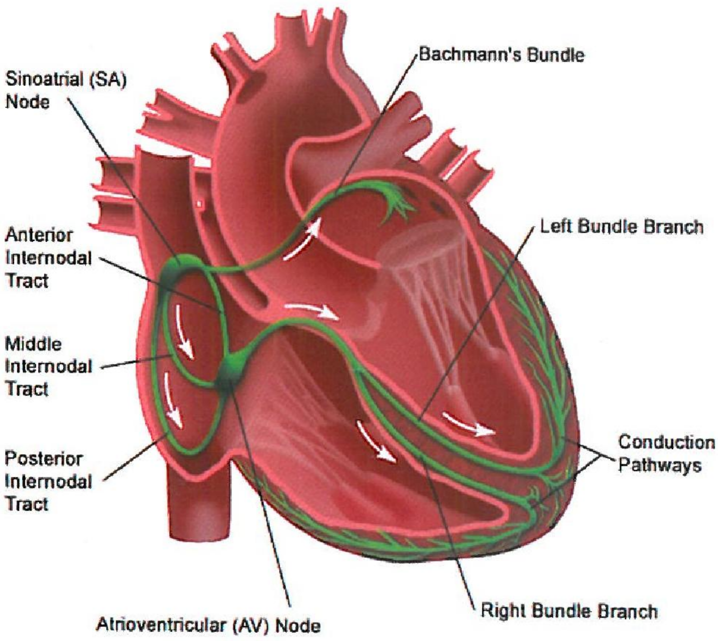
- **Arrhythmias** [uh-RITH-me-uhs] *is defined as*;
  - Loss of cardiac rhythm *or* abnormal heart rhythm.
- **Cardiac arrhythmia**, *also known as* **cardiac dysrhythmia** *or* **irregular heartbeat**, is a group of conditions in which the heartbeat is irregular, **too fast** *or* **too slow**.
  - A **fast** heart rate (in adults, more than 100 beats per minute) is called **tachycardia**.
  - A **slow** heart rate (in adults, less than 60 beats per minute) is called **bradycardia**.
- ***Many*** **arrhythmias have *no* symptoms**. When symptoms are present these may include palpitations or feeling a pause between heartbeats.
- *Arrhythmia prevalence*;
  - Arrhythmias affect millions of people.
  - In Europe and North America, as of 2014, atrial fibrillation affects about 2-3% of the population.
  - Atrial fibrillation and atrial flutter resulted in 112,000 deaths in 2013, up from 29,000 in 1990.
  - Sudden cardiac death is the cause of about half of deaths due to cardiovascular disease or about 15% of all deaths globally.
  - About 80% of sudden cardiac death is the result of ventricular arrhythmias.
  - Arrhythmias may occur at any age but are more common among older people.



➢ Electrical Conduction System of the Heart:-

- Structure;

- ***Normally***, **the 4 chambers** of the heart (2 atria and 2 ventricles) **contract in a very specific coordinated manner**.
- **The electrical impulse** that signals heart to contract in a synchronized manner ***begins*** in the **sinoatrial node (SA node)**.
- The signal leaves the SA node and ***travels through*** the **2 upper chambers (atria)**.
- Then the signal ***passes through*** another node; **atrioventricular node (AV node)** and ***finally***, through the **lower chambers** (ventricles).
- ***The result*** is that the **chambers contract in a coordinated fashion**.
- ***Problems*** can occur anywhere along this conduction system, causing **various arrhythmias**.

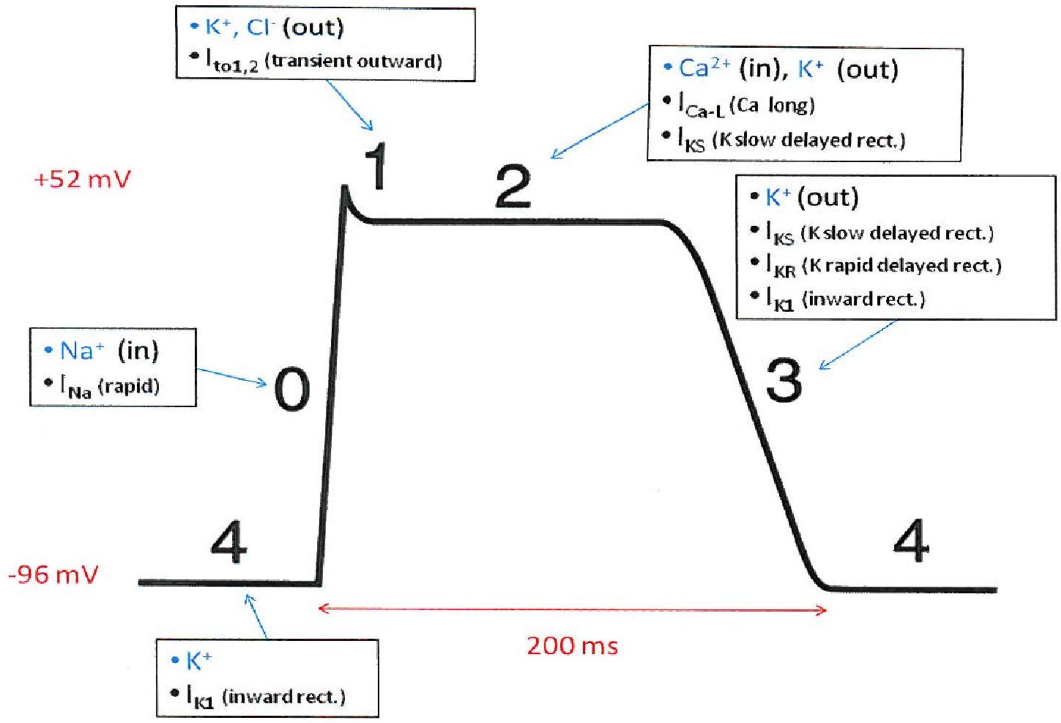


Electrical System of the Heart

Sinoatrial (SA) Node
Bachmann's Bundle
Anterior Internodal Tract
Left Bundle Branch
Middle Internodal Tract
Conduction Pathways
Posterior Internodal Tract
Atrioventricular (AV) Node
Right Bundle Branch

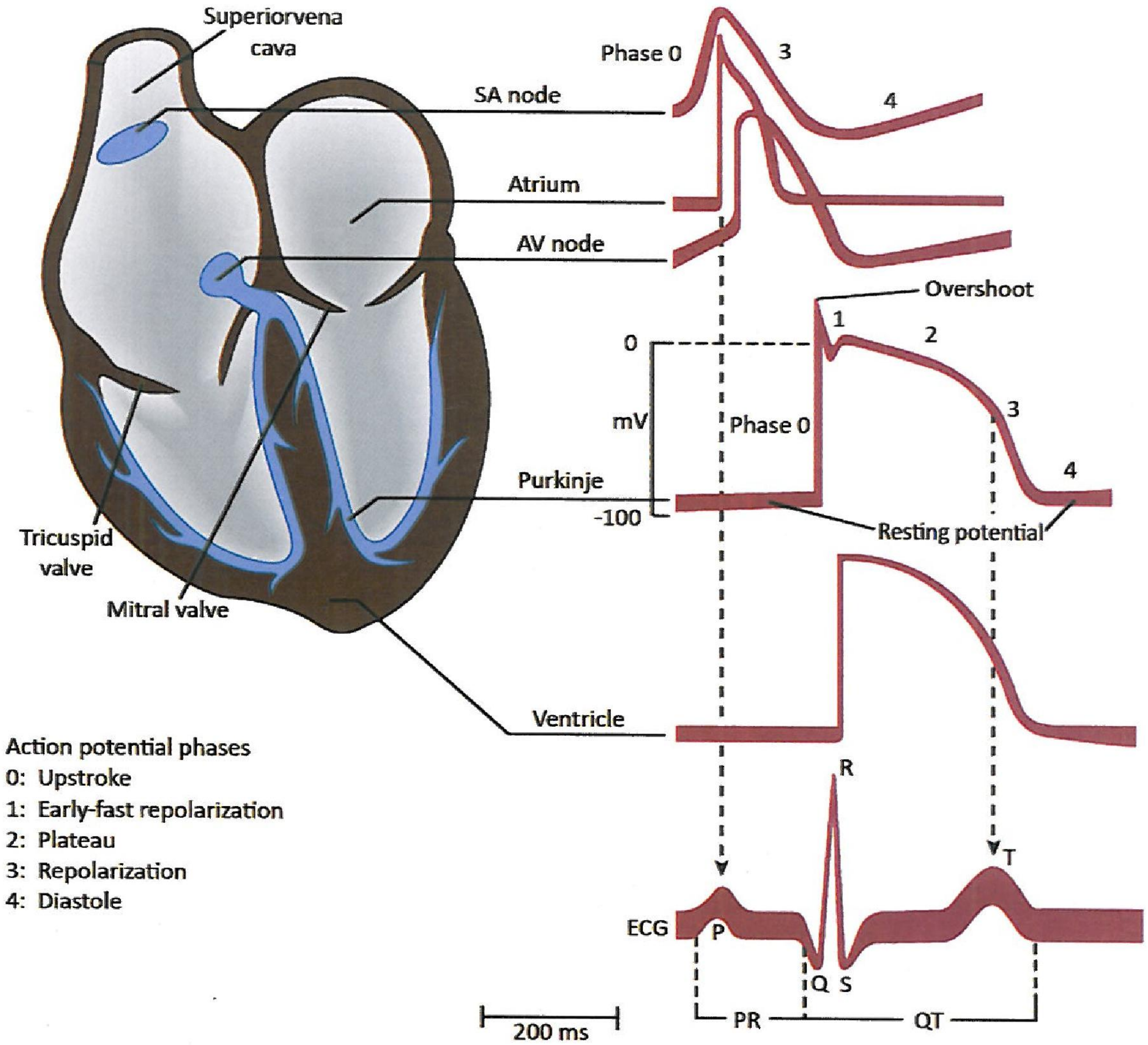
- Electrochemical Mechanism (Cardiac Action Potential);

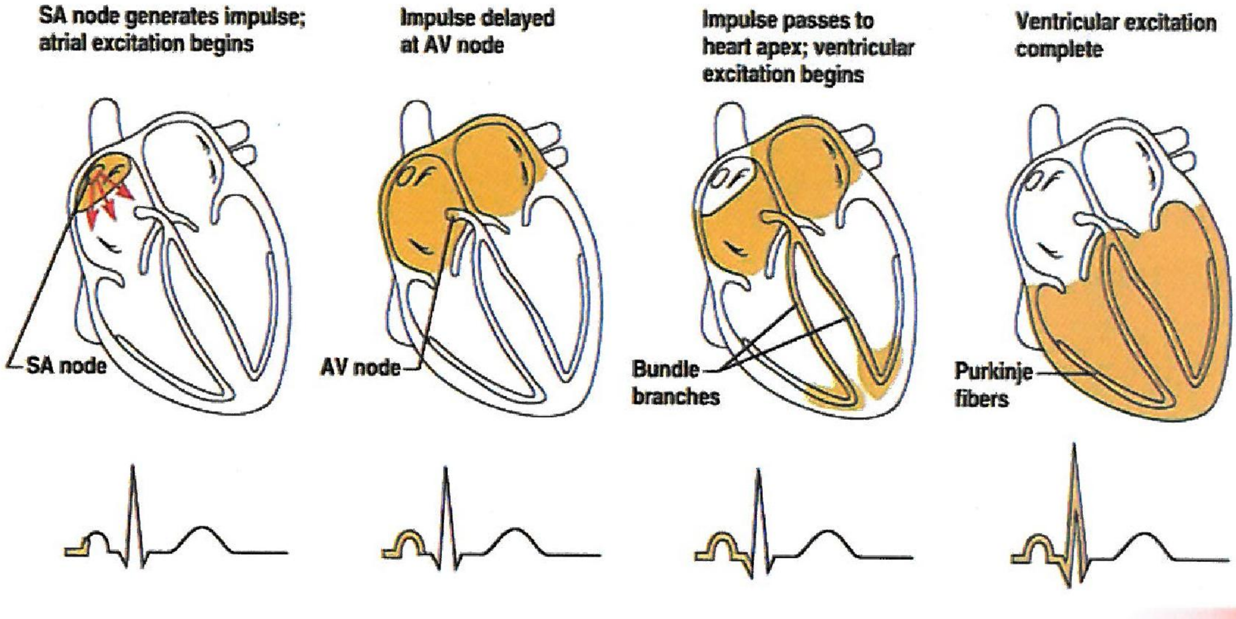
- Cardiac muscle has some similarities to neurons and skeletal muscle, as well as important unique properties. Like a neuron, a given myocardial cell has a negative membrane potential when at rest. Stimulation above a threshold value induces the opening of voltage-gated ion channels and a flood of cations into the cell.
- The transmembrane potential of cardiac cells is determined by the ***concentration*** of several ions chiefly, Na^+, K^+, Ca^{2+}, Cl^- on either side of the membrane and the ***permeability*** of the membrane to each ion.

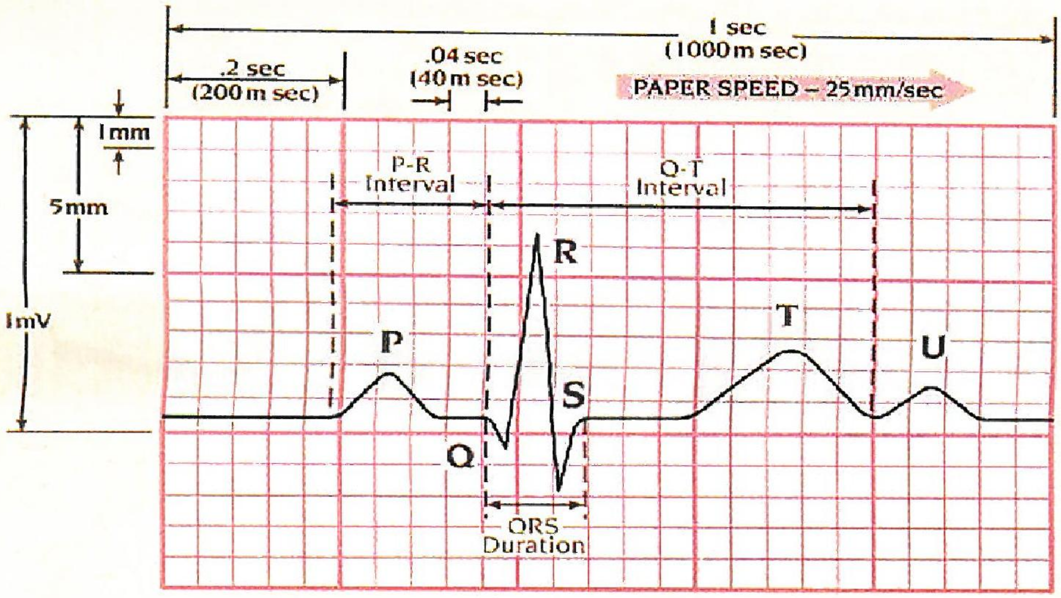

• K^+, Cl^- (out)
• $I_{to1,2}$ (transient outward)
• Ca^{2+} (in), K^+ (out)
• I_{Ca-L} (Ca long)
• I_{KS} (K slow delayed rect.)
+52 mV
1
2
• K^+ (out)
• I_{KS} (K slow delayed rect.)
• I_{KR} (K rapid delayed rect.)
• I_{K1} (inward rect.)
• Na^+ (in)
• I_{Na} (rapid)
0
3
4
-96 mV
4
200 ms
• K^+
• I_{K1} (inward rect.)

- **The action potential has 5 phases** (numbered 0-4);
  - **Phase 4** (**Resting Membrane Potential**; **RMP**);
    - Is the membrane potential when the cell is not being stimulated.
    - So in the standard myocyte model this phase will be a horizontal line.
    - It is associated with heart diastole (relaxation) so is called diastolic depolarization.
    - The normal resting membrane potential in the ventricular myocardium is about -85 to -95 mV (millivolts); (the -ve sign indicates the type of charge inside the cell that predominant).
    - The membrane is most permeable to K^+ and relatively impermeable to other ions.
  - **Phase 0** (**Rapid Depolarization**);
    - Opening of the fast Na^+ channels causing a rapid increase in the membrane conductance to Na^+ and thus a rapid influx of Na^+ ions into the cell.
    - The membrane potential is reversed from negative to positive and peaks at about +25mV inside the cell.
  - **Phase 1** (**Partial Repolarization**);
    - Inactivation of the fast Na^+ channels.
    - Movement of Cl^- ions across the cell membrane as a result of the change in membrane potential, and K^+ efflux.
  - **Phase 2** (**Plateau**);
    - Cardiac action potential is sustained by a balance between inward movement of Ca^{2+} through L-type calcium channels and outward movement of K+ through the *slow delayed* K channel.
  - **Phase 3** (**Rapid Repolarization**);
    - The L-type Ca^{2+} channels close, while the slow delayed K+ channels remain open as more potassium leak channels open.
    - The delayed K+ channels close when the membrane potential is restored to about -85 to -90 mV.

- Conduction of the impulse through the heart, with the corresponding electrocardiogram (ECG) trace;


Superiorvena cava
SA node
Atrium
AV node
Tricuspid valve
Mitral valve
Purkinje
Ventricle
Phase 0
3
4
Overshoot
1
2
0
mV
Phase 0
3
4
-100
Resting potential
R
T
ECG
P
Q
S
PR
QT
200 ms
Action potential phases
0: Upstroke
1: Early-fast repolarization
2: Plateau
3: Repolarization
4: Diastole


SA node generates impulse; atrial excitation begins
Impulse delayed at AV node
Impulse passes to heart apex; ventricular excitation begins
Ventricular excitation complete
SA node
AV node
Bundle branches
Purkinje fibers



VERTICAL AXIS	
	1 Small Square = 1 mm (0.1 mV)
	1 Large Square = 5mm (0.5mV)
	2 Large Squares = 1mV

HORIZONTAL AXIS	
	1 Small Square = .04 sec (40 m sec)
	1 Large Square = .2 sec (200 m sec)
	5 Large Squares = 1 sec (1000 m sec)

Electrocardiogram (ECG)

- ECG or EKG (from the German Elektrokardiogramm).
- ECG is used to measure the rate and regularity of heartbeats.
- Impulses are recorded as waves displayed on a monitor or printed on graph paper.
  - All of the waves on an ECG tracing and the intervals between them have a predictable time duration, a range of acceptable amplitudes (voltages), and a typical morphology.
  - For ease of measuring the amplitudes and intervals, an ECG is printed on graph paper at a standard scale:
    - Each 1 mm (one small box) ⇨ 40 milliseconds of time on the x-axis and 0.1 millivolts on the y-axis.

Feature	Description
RR interval	The interval between an R wave and the next R wave.
P wave	During normal atrial depolarization, the main electrical vector is directed from the SA node towards the AV node, and spreads from the right atrium to the left atrium. This turns into the P wave on the ECG.
PR interval	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex. The PR interval reflects the time the electrical impulse takes to travel from the SA node through the AV node and entering the ventricles.
PR segment	The PR segment connects the P wave and the QRS complex.
QRS complex	The QRS complex reflects the rapid depolarization of the right and left ventricles. They have a large muscle mass compared to the atria, so the QRS complex usually has much larger amplitude than the P-wave.
J-point	The point at which the QRS complex finishes and the ST segment begins, it is used to measure the degree of ST elevation or depression present.
ST segment	The ST segment connects the QRS complex and the T wave. The ST segment represents the period when the ventricles are depolarized.
T wave	The T wave represents the repolarization (or recovery) of the ventricles
ST interval	The ST interval is measured from the J point to the end of the T wave.
QT interval	The QT interval is measured from the beginning of the QRS complex to the end of the T wave. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.
U wave	The U wave is hypothesized to be caused by the repolarization of the interventricular septum.

➢ Causes of Arrhythmias:-

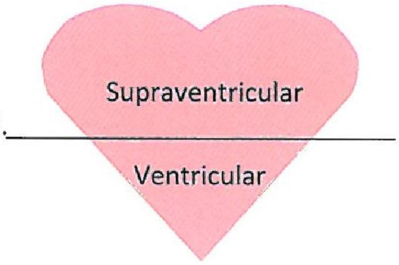
- Cardiac arrhythmias are a common problem in clinical practice occurring in up to 25% of patients treat with digitalis, 50% of anesthetized patients and over 80% of patients with acute myocardial infarction, the most common causes of arrhythmias;
    - Heart attack (myocardial infarction).
    - Changes in heart structure.
    - Coronary artery diseases.
    - Diabetes and hypertension.
    - Smoking and stress.
    - Drinking too much alcohol or caffeine.
    - Drug abuse and electrolytes imbalance.
    - Certain medications (such as digitalis).
    - Overactive thyroid gland (hyperthyroidism) or underactive thyroid gland (hypothyroidism).

➢ Symptoms of Arrhythmia:-

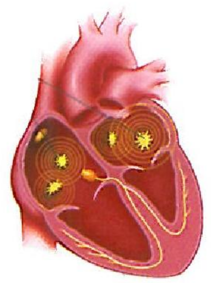
- Arrhythmias may not cause any signs or symptoms.
- If symptoms are present these may include;
    - Fast or slow heartbeat.
    - Skipping beats.
    - Fainting, lightheadedness and dizziness.
    - Shortness of breath and chest pain.

➢ Classification of Arrhythmias:-

- Arrhythmia may be classified by;
    - **Site of impulse formation** (atrial, junction or ventricles).
    - **Rate** (tachycardia or bradycardia).
    - **Mechanism** (automaticity, re-entry or triggered).
    - **Duration** (isolated premature beats).

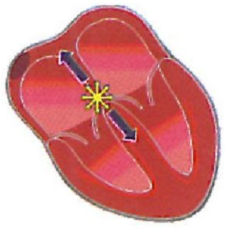


o According to site of impulse formation:



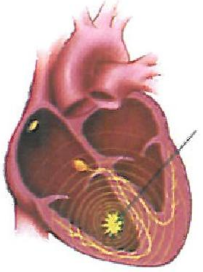
Atrial

- Premature Atrial Contractions (PACs).
- Wandering Atrial Pacemaker.
- Multifocal atrial tachycardia.
- Atrial flutter.
- Atrial fibrillation (A-fib).



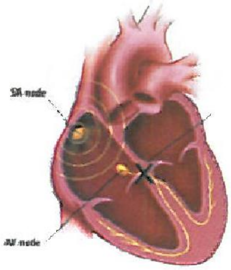
Junctional

- Supraventricular tachycardia (SVT).
- AV nodal re-entrant tachycardia.
- Junctional rhythm.
- Junctional tachycardia.
- Premature Junctional contraction.



Ventricular

- Premature Ventricular Contractions (PVC).
- Accelerated idioventricular rhythm.
- Monomorphic Ventricular tachycardia.
- Polymorphic ventricular tachycardia.
- Ventricular fibrillation.

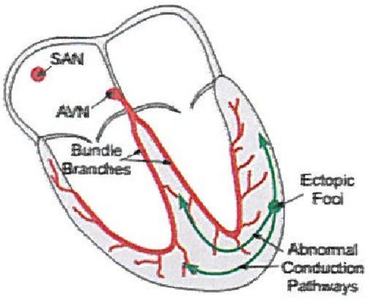


Heart blocks

- First degree.
- Second degree.
- Third degree.

- *N.B.*: **Sudden Arrhythmic Death Syndrome (SADS)**; used to describe sudden death due to cardiac arrest brought on by an arrhythmia.

○ According to Mechanism:



- **Automaticity** (Ectopic pacemaker or Ectopic focus); excitable group of cells that causes a premature heart beat outside the normally functioning SA node.
- **Re-entry**; electrical impulse recurrently travels in a tight circle within the heart.
- **Fibrillation** (atrial fibrillation or ventricular fibrillation).

○ According to Heart Rate:

- **Tachycardia**
- **Bradycardia**
- **Premature Heartbeats**
- **Heart block**

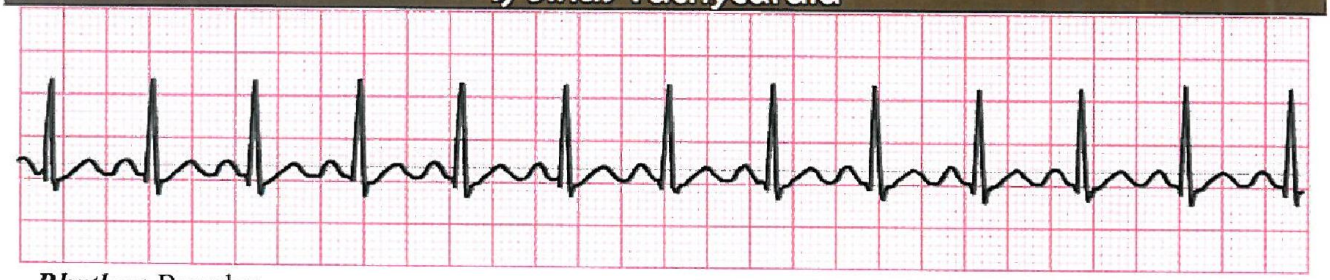
I) Tachycardia

- Tachycardia; resting heart rate greater than 100 beats a minute.

A) Supraventricular

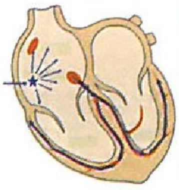
- It is a type of tachycardia originating at or above the atrioventricular node.

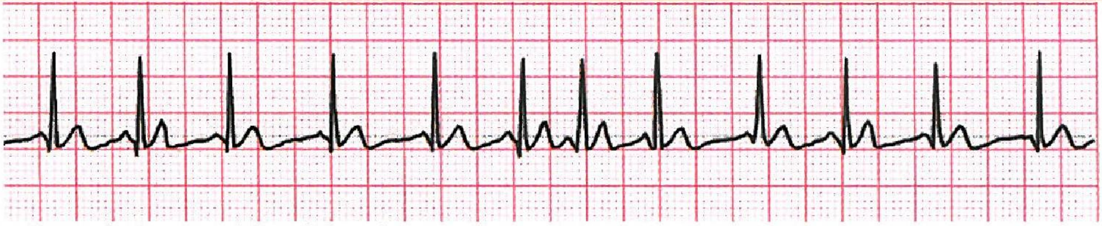
1) Sinus Tachycardia



- ***Rhythm***; Regular.
- ***Rate***; Fast (> 100 bpm).
- ***P Wave***; Normal, may merge with T wave at very fast rates.
- ***PR Interval***; Normal (0.12-0.20 sec).
- ***QRS***; Normal (0.06-0.10 sec).
- ***Notes***; QT interval shortens with increasing heart rate.

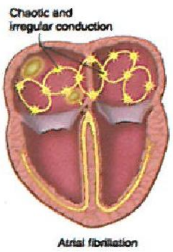
2) Atrial Tachycardia

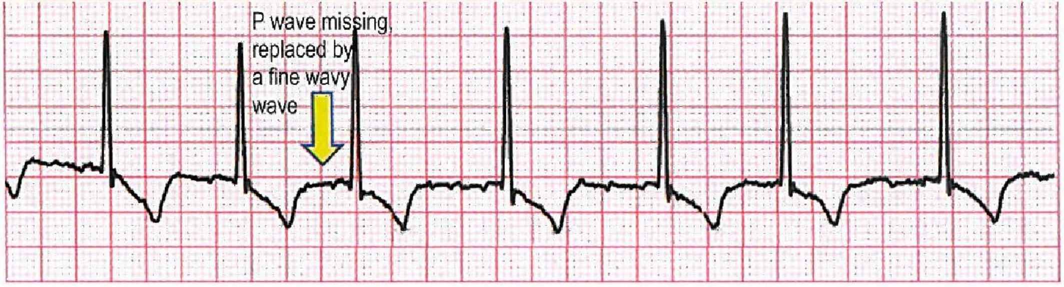




- ***Origin***; within the atria but outside of the sinus node.
- ***Rhythm***; Irregular
- ***Rate***; Fast (> 100 bpm)
- ***P Wave***; Often changing shape and size from beat to beat (at least three differing forms).
- ***PR Interval***; Variable
- ***QRS***; Normal (0.06-0.10 sec).
- ***Notes***; T wave is often distorted Also review wandering atrial pacemaker lesson.

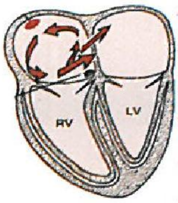
3) Atrial Fibrillation (AF or A-fib)

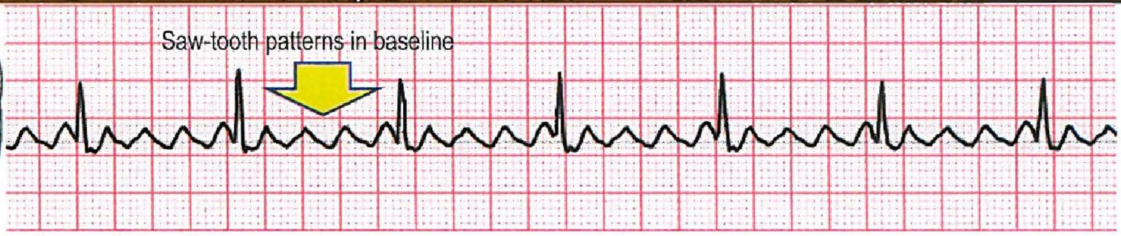

Chaotic and irregular conduction
Atrial fibrillation


P wave missing replaced by a fine wavy wave

- ***Rhythm***; Irregular.
- ***Rate***; Very fast (> 350 bpm) for Atrial, but ventricular rate may be slow, normal or fast.
- ***P Wave***; Absent - erratic waves are present.
- ***PR Interval***; Absent.
- ***QRS***; Normal but may be widened if there are conduction delays.

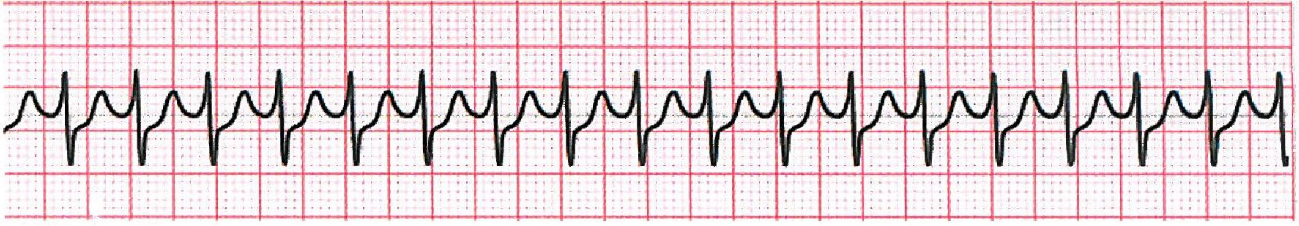
4) Atrial Flutter




Saw-tooth patterns in baseline

- ***Rhythm***; Regular or irregular.
- ***Rate***; Fast (250-350 bpm) for Atrial, but ventricular rate is often slower.
- ***P Wave***; Not observable, but **saw-toothed flutter waves** are present.
- ***PR Interval***; Not measureable.
- ***QRS***; Normal (0.06-0.10 sec).

5) Supraventricular Tachycardia (SVT)

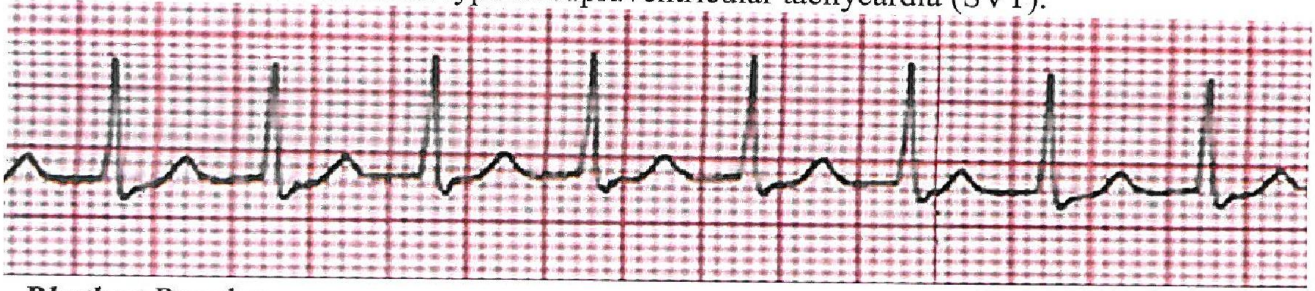


- ***Rhythm***; Regular
- ***Rate***; Fast (150-250 bpm)
- ***P Wave***; Merged with T wave
- ***PR Interval***; Normal (0.12 sec)
- ***QRS***; Normal (0.10 sec)
- ***Notes***; PR interval can be difficult to measure.

- ***Types of Supraventricular Tachycardia***;
    - Atrioventricular nodal reentrant tachycardia (AVNRT).
    - Atrioventricular reciprocating tachycardia (AVRT).
        - Wolff-Parkinson-White syndrome (a type of AVRT).

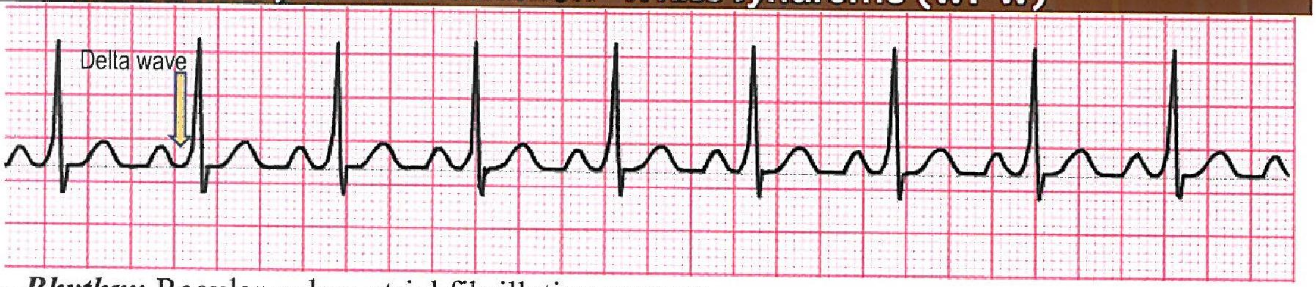
6) AV Nodal Reentrant Tachycardia (AVNRT)

- AVNRT is the most common type of supraventricular tachycardia (SVT).



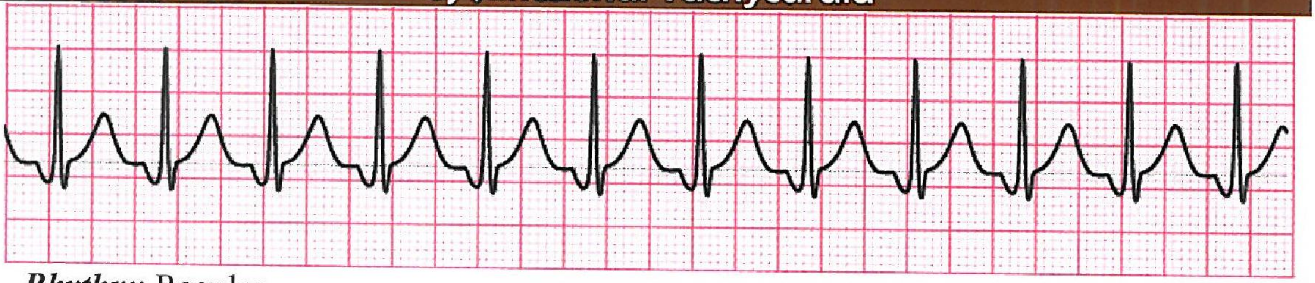
- ***Rhythm***; Regular.
- ***Rate***; Fast.
- ***P Wave***; No visible P waves or visible after the QRS or before the QRS.

7) Wolff–Parkinson–White syndrome (WPW)



- ***Rhythm***; Regular unless atrial fibrillation present.
- ***Rate***; Normal (60-100 bpm).
- ***P Wave***; Normal.
- ***PR Interval***; Can be short (<0.12 sec).
- ***QRS***; Usually wide (> 0.12 sec).
- ***Notes***; delta wave distorts the early part of the QRS complex.

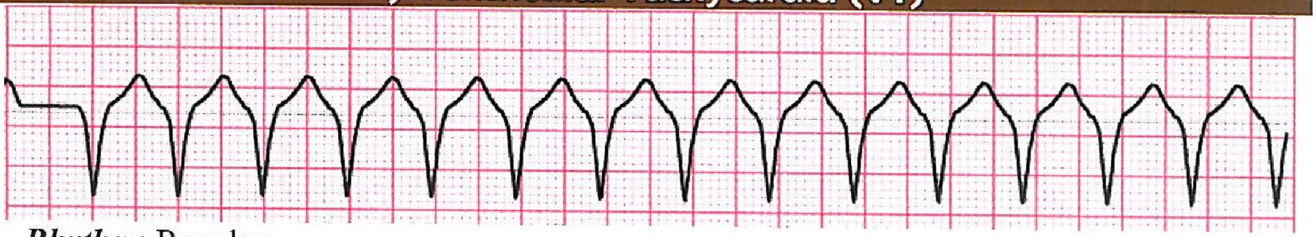
8) Junctional Tachycardia



- ***Rhythm***; Regular.
- ***Rate***; Fast (100-180 bpm).
- ***P Wave***; Present before, during (hidden) or after QRS, if visible it is inverted.
- ***PR Interval***; Absent or short.
- ***QRS***; Normal (0.06-0.10 sec).

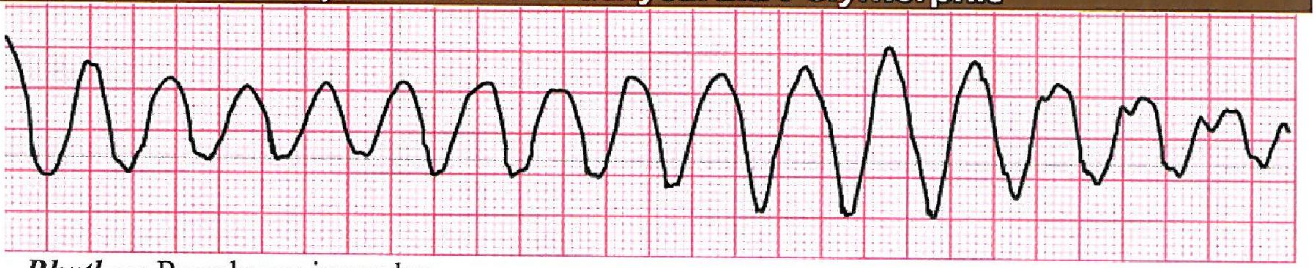
B) Ventricular

1) Ventricular Tachycardia (VT)



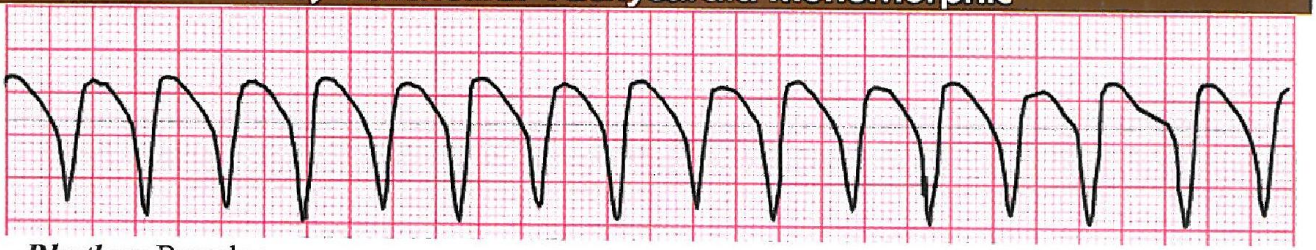
- ***Rhythm***; Regular.
- ***Rate***; Fast (100-250 bpm).
- ***P Wave***; Absent.
- ***PR Interval***; Not measurable.
- ***QRS***; Wide (>0.10 sec), bizarre appearance.

2) Ventricular Tachycardia Polymorphic



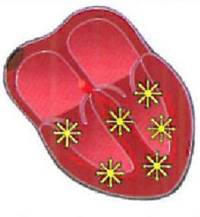
- ***Rhythm***; Regular or irregular.
- ***Rate***; Fast (100-300 bpm).
- ***P Wave***; Absent.
- ***PR Interval***; Not measurable.
- ***QRS***; Normal or wide (>0.10 sec), bizarre looking.

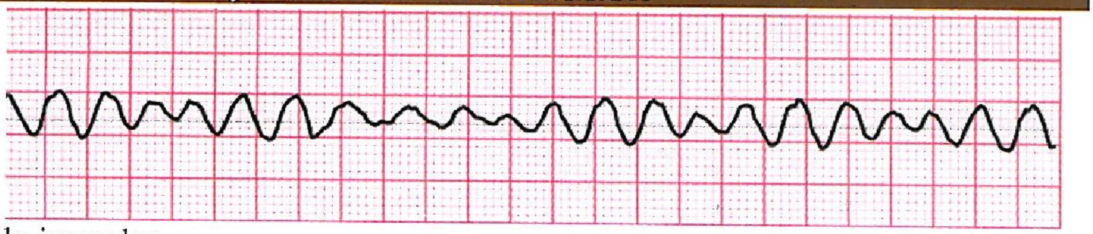
3) Ventricular Tachycardia Monomorphic



- ***Rhythm***; Regular.
- ***Rate***; Fast (100-250 bpm).
- ***P Wave***; Absent.
- ***PR Interval***; Not measurable.
- ***QRS***; Wide (>0.10 sec), bizarre looking.

4) Ventricular Fibrillation



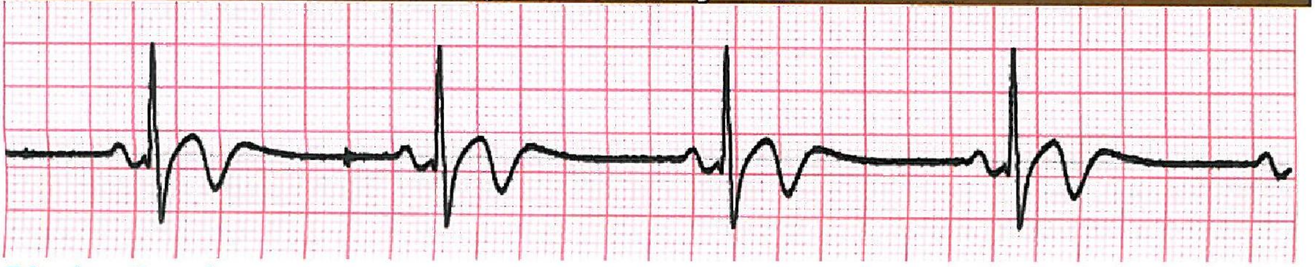


- ***Rhythm***; Highly irregular.
- ***Rate***; Unmeasurable.
- ***P Wave***; Absent.
- ***PR Interval***; Not measurable.
- ***QRS***; None.
- ***Notes***; ECG tracings is a wavy line.

II) Bradycardia

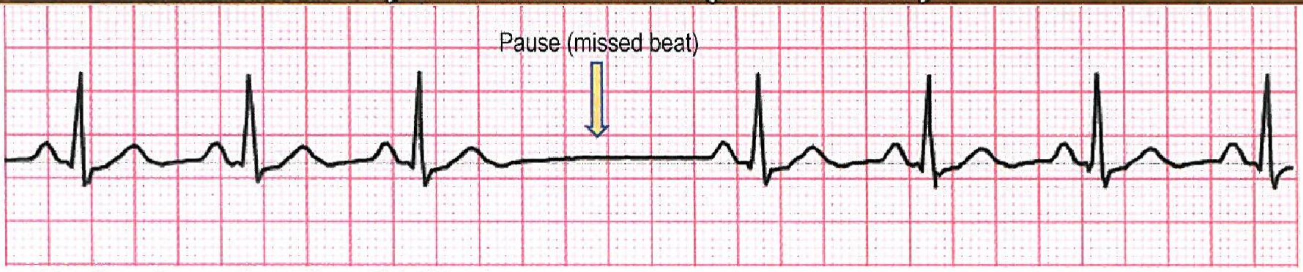
- Bradycardia; resting heart rate less than 60 beats a minute.

1) Sinus Bradycardia



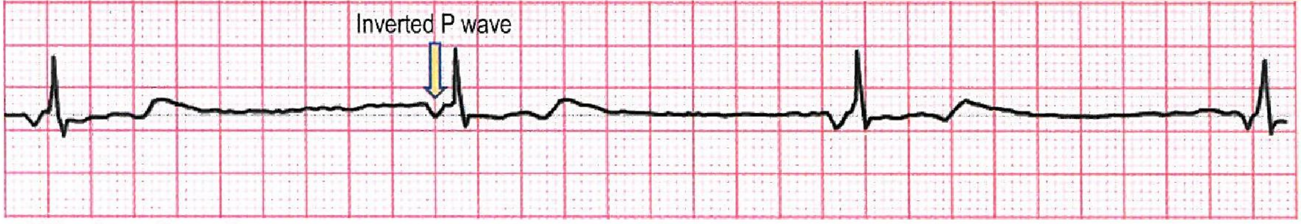
Rhythm; Regular.
Rate; Slow (< 60 bpm).
P Wave; Normal.
PR Interval; Normal (0.12-0.20 sec).
QRS; Normal (0.06-0.10 sec).

2) Sinoatrial Block (Sinus Pause)



- ***Rhythm***; Irregular when SA block occurs.
- ***Rate***; Normal or slow.
- ***P Wave***; Normal.
- ***PR Interval***; Normal (0.12-0.20 sec).
- ***QRS***; Normal (0.06-0.10 sec).
- ***Notes***; Pause time is an integer multiple of the P-P interval Try to identify specific type of atrial tachycardia - see other pages.

3) Junctional Escape Rhythm



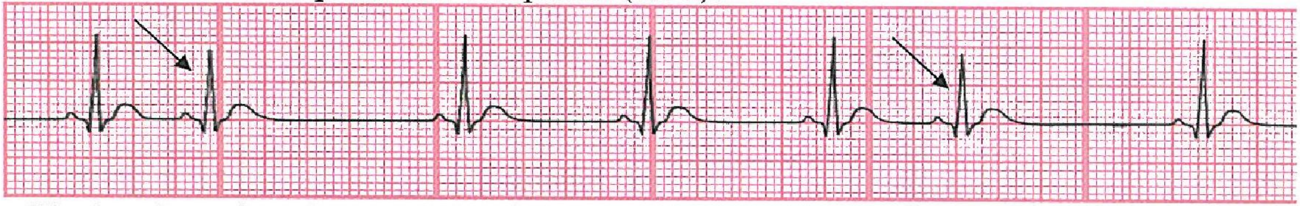
- ***Rhythm***; Regular.
- ***Rate***; Slow (40-60 bpm).
- ***P Wave***; Present before, during (hidden) or after QRS, if visible it is inverted.
- ***PR Interval***; Not measurable.
- ***QRS***; Normal (0.06-0.10 sec).

III) Premature Heartbeats

- It is a beat that occurs earlier than expected.

1) Premature Atrial Contraction (PAC)

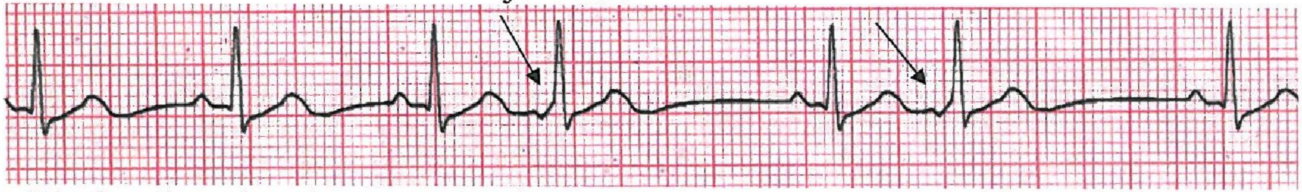
- Also known as atrial premature complexes (APC).



- ***Rhythm***; Irregular when premature beat occurs.
- ***P Wave***; Shaped.
- ***QRS***; Normal.

2) Premature Junctional Contraction (PJC)

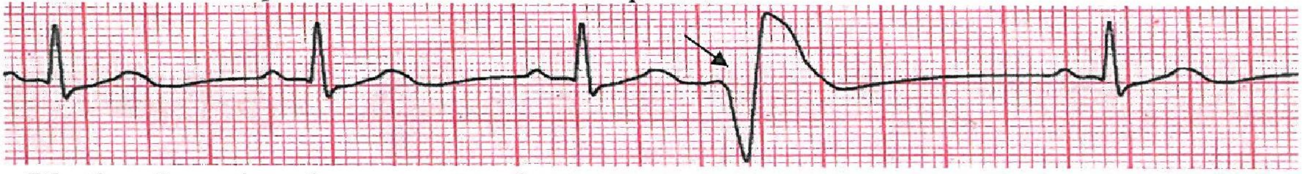
- Premature junctional contraction (PJC) are premature cardiac electrical impulses originating from the AV node of the heart or "junction."



- ***Rhythm***; Irregular when premature beat occurs.
- ***P Wave***; Absent in premature beats.
- ***QRS***; Normal.

3) Premature Ventricular Contraction (PVC)

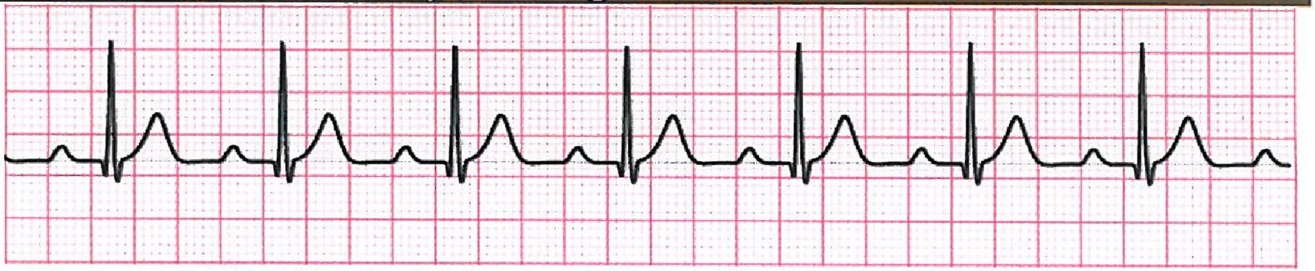
- Also known as a premature ventricular complex.



- ***Rhythm***; Irregular when premature beat occurs.
- ***P Wave***; Absent in premature beats.
- ***T wave***; Inverted in premature beats.
- ***QRS***; Wide in premature beats.

IV) Heart Block

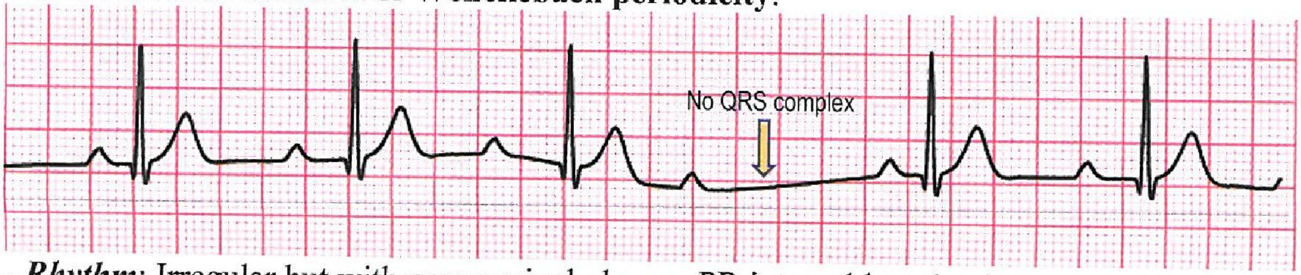
1) First Degree Heart Block



- ***Rhythm***; Regular.
- ***Rate***; The underlying rate.
- ***P Wave***; Normal.
- ***PR Interval***; Prolonged (>0.20 sec).
- ***QRS***; Normal (0.06-0.10 sec).
- ***Notes***; A first degree AV block occurs when electrical impulses moving through the AV node are delayed (but not blocked). First degree indicates slowed conduction without missed beats.

2) Second Degree Heart Block Type I

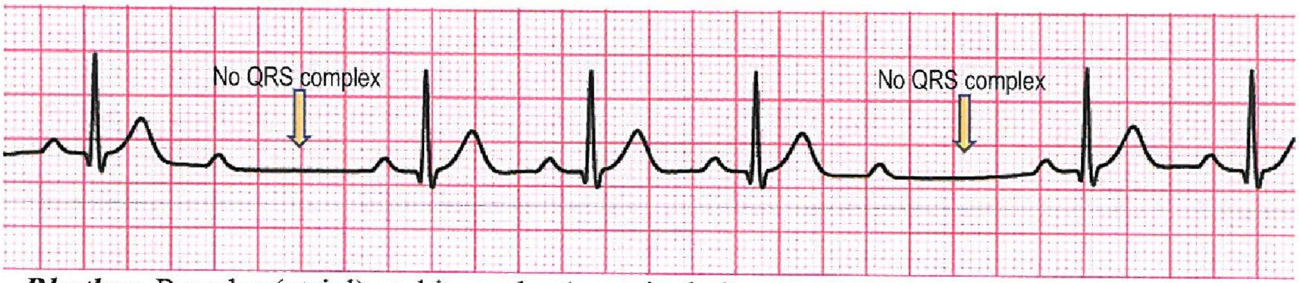
- Also known as **Mobitz I** or **Wenckebach periodicity**.



- ***Rhythm***; Irregular but with progressively longer PR interval lengthening.
- ***Rate***; The underlying rate.
- ***P Wave***; Normal.
- ***PR Interval***; Progressively longer until a QRS complex is missed, then cycle repeats.
- ***QRS***; Normal (0.06-0.10 sec).

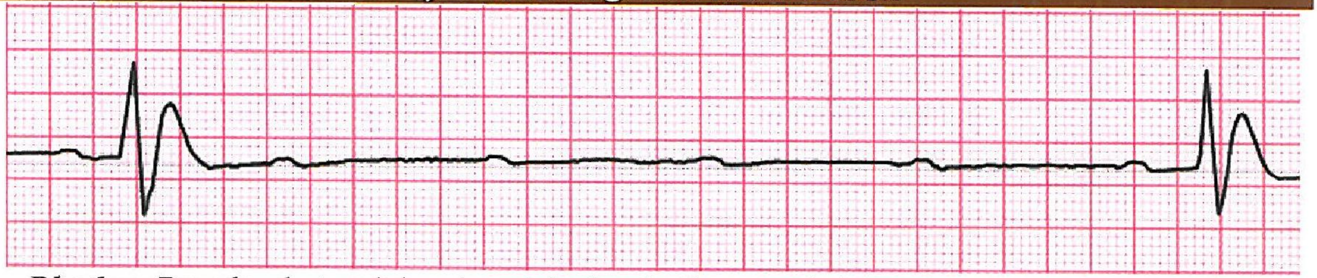
3) Second Degree Heart Block Type II

- Also known as **Mobitz II**.



- ***Rhythm***; Regular (atrial) and irregular (ventricular).
- ***Rate***; Characterized by Atrial rate usually faster than ventricular rate (usually slow).
- ***P Wave***; Normal form, but more P waves than QRS complexes.
- ***PR Interval***; Normal or prolonged.
- ***QRS***; Normal or wide.

4) Third Degree Heart Block



- ***Rhythm***; Regular, but atrial and ventricular rhythms are independent.
- ***Rate***; Characterized by atrial rate usually normal and faster than ventricular rate.
- ***P Wave***; Normal shape and size, may appear within QRS complexes.
- ***PR Interval***; Absent: the atria and ventricles beat independently.
- ***QRS***; Normal, but wide if junctional escape focus.

Antiarrhythmic Drugs

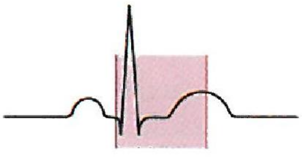
Goals of Antiarrhythmic Drugs:-

- The ultimate goal of antiarrhythmic drug therapy is to ***restore*** **normal rhythm** and **conduction of the heart**.

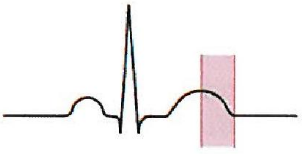
Singh Vaughan Williams Classification:-

- The Singh Vaughan Williams classification was introduced in 1970. As a doctoral candidate at Oxford University working in the lab of Vaughan Williams.
- *Dr. Bramah Singh* determined that Amiodarone and Sotalol had antiarrhythmic properties and belonged to a new class of antiarrhythmic agents.
- There are 5 main classes in the Singh Vaughan Williams classification:
  - **Class I**; agents interfere with the sodium (Na^+) channel.
  - **Class II**; agents are anti-sympathetic nervous system agents.
  - **Class III**; agents affect potassium (K^+) efflux.
  - **Class IV**; agents affect calcium channels and the AV node.
  - **Class V**; agents work by other or unknown mechanisms.

Class/Ion Affected	Agents	Physiologic Effect	Result on Electrophysiologic Parameters	Clinical Utility
Class I (Na^+ channel blockers)				
IA (intermediate)	Quinidine Disopyramide Procainamide	↓ Conduction velocity ↑ Refractory period	↑ QRS complex and ↑ QT interval	Atrial and ventricular arrhythmias
IB (fast)	Lidocaine Mexiletine	↓ Conduction velocity ↓ Refractory period	↓ QT interval	Ventricular arrhythmias
IC (slow)	Flecainide Propafenone	↓↓↓ Conduction velocity Ø Refractory period	↑ QRS complex	Supraventricular arrhythmias and ventricular arrhythmias
Class II (β-Blockers)	Metoprolol Esmolol Atenolol	↓ Conduction velocity ↑ Refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias
Class III (K^+ channel blockers)	Amiodarone Dronedarone Sotalol Dofetilide Ibutilide	Ø Conduction velocity ↑↑↑ Refractory period	↑ QT interval	Atrial and ventricular arrhythmias
Class IV (Ca^{2+} channel blockers)	Diltiazem verapamil	↓ Conduction velocity ↑ Refractory period	↓ HR and ↑ PR interval	Atrial and ventricular arrhythmias



Absolute Refractory Period



Relative Refractory Period

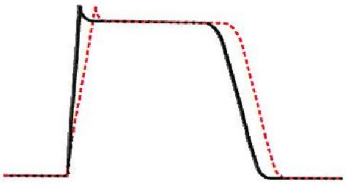
1) Class I (Sodium Channel Blockers)

A) Class IA

Quinidine (Quinacard®)	**Procainamide** (Pronestyl®)	**Disopyramide** (Norpace®)

- **Quinidine** [KWIN-i-deen] is the prototype class IA drug. Other agents in this class include **Procainamide** [proe-KANE-a-mide] and **Disopyramide** [dye-soe-PEER-a-mide].

Mechanism OF Action



- By blocking sodium channels, prevents sodium influx, thus slowing the rapid upstroke during phase 0.
- Decreases the slope of phase 4 spontaneous depolarization, inhibits potassium channels and blocks calcium channels.
- Because of these actions, it ***slows*** **conduction velocity** and ***increases*** **refractoriness (*prolongs* QRS duration)**.

Pharmaco Kinetics

- **Quinidine sulfate** or **gluconate**; rapidly completely absorbed after oral administration. It extensive metabolism primarily by the CYP3A4.
- **Procainamide**; is available in an IV formulation only (in US) and it is a short duration of action. A portion of procainamide is acetylated in the liver to N-acetylprocainamide (NAPA), which prolongs the duration of the action potential. Thus, NAPA has properties and side effects of a class III drug. NAPA is eliminated via the kidney and dosages may need to be adjusted in patients with renal failure.
- **Disopyramide**; absorbed well after oral administration. It is metabolized in the liver (CYP3A4), about half of the drug is excreted unchanged by the kidneys.

Therapeutic Uses

- **Quinidine**; **Atrial fibrillation/flutter** and **ventricular tachycardia**.
  - ***Dose***; As Sulfate: 200–400 mg orally every 6 hours.
    As Gluconate (CR): 324 mg orally every 8-12 hours.
- **Procainamide**; **Atrial fibrillation/flutter conversion**: 1 g IV for 30 min; then 2 mg/min.
  - **Ventricular tachycardia conversion**: 20 mg/min IV until 17 mg/kg or arrhythmia is controlled.
  - **Ventricular tachycardia maintenance**: 1-4 mg/min.
    (reduce dose in renal and liver dysfunction)
- **Disopyramide**; **Atrial fibrillation/flutter conversion**: Immediate-release (IR) 200 mg (if <50 kg) or 300 mg (if >50 kg) orally/6 hours.
  - **Atrial fibrillation/flutter maintenance**: IR 150 mg orally every 6 hours or as controlled release (CR) 300 mg orally every 12 hours, dose adjustment if; <50 kg, moderate renal dysfunction or hepatic dysfunction.

Side Effects

- **Quinidine**; ***common side effects***; nausea, vomiting, diarrhea (30%) and **Cinchonism** or **Quinism** (blurred vision, tinnitus, headache, disorientation, and psychosis).
- **Procainamide**; ***common side effects***; hypotension (IV use, 5%).
  - ***Chronic use*** of procainamide may induce production of an antinuclear antibody (ANA) in up to 70% of asymptomatic patients after 6 weeks of therapy. This antibody may be associated with a reversible lupus-like syndrome (myalgias, arthralgias, arthritis, and pulmonary or pericardial serositis) in rare cases.
- **Disopyramide**; ***common side effects***; anticholinergic effects (dry mouth, urinary retention, blurred vision, and constipation).
- ***Both*** **Quinidine** and **Disopyramide** should be used with caution with potent inhibitors of CYP3A4.

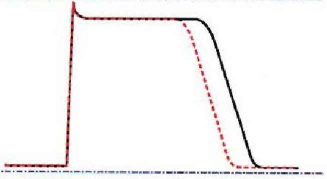
B) Class IB

Lidocaine (LidoPen®)	**Mexiletine** (Mexitil®)

- **Lidocaine** [LYE-doe-kane] and **Mexiletine** [MEX-i-le-teen] are class IB agents.

Mechanism Of Action

- In addition to sodium channel blockade, lidocaine and mexiletine ***shorten*** **phase 3 repolarization** and ***decrease*** the **duration of the action potential**.



Pharmaco Kinetics

- **Lidocaine**;
  - ***First-pass effect***; Lidocaine is given IV because of extensive first-pass hepatic metabolism, only 3% of orally administered lidocaine appears in the plasma.
  - ***Metabolism***; The drug is dealkylated to two less active metabolites, primarily by CYP1A2 with a minor role by CYP3A4.
  - ***Half-life***; 1-2 hours.
  - ***Dose***; loading dose; 150-200 mg slow bolus over about 15 min.
    Maintenance infusion; 2-4 mg/min. to achieve a therapeutic plasma level 2-6 mcg/mL.
  - Drugs that lower hepatic blood flow (β-blockers) may require lidocaine dose adjustment.
- **Mexiletine**;
  - ***Absorption and metabolism***; Mexiletine is well absorbed after oral administration. It is metabolized in the liver primarily by CYP2D6 to inactive metabolites and excreted mainly via the biliary route.
  - ***Half-life***; 8-20 hours.
  - ***Dose***; 200-300 mg orally every 8 hours, maximum 1200 mg/day.

Therapeutic Uses

- **Lidocaine** is the ***agent of choice*** for ***termination*** of **ventricular tachycardia** and ***prevention*** of **ventricular fibrillation after acute myocardial infarction**.
- **Mexiletine** is indicated for the *treatment* of **ventricular tachycardia**.

Side Effects

- **Lidocaine** has a **wide therapeutic index**, ***common side effects***; CNS effects; nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion and convulsions.
- **Mexiletine** has a **narrow therapeutic index** and caution should be used when administering the drug with inhibitors of CYP2D6, ***common side effects***; nausea, vomiting, and dyspepsia.

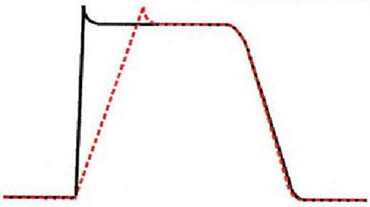
C) Class IC

Flecainide (Tambocor®)	**Propafenone** (Rythmol®)

- **Flecainide** [FLEK-a-nide], **Propafenone** [proe-PA-fen-one] are class IC agents.

Mechanism Of Action

- ***Suppresses*** **phase 0 upstroke in Purkinje and myocardial fibers**. This causes **marked** ***slowing*** of **conduction in all cardiac tissue**, with a **minor** **effect** on the **duration of the action potential** and **refractoriness**.



- **Flecainide** also blocks potassium channels *but* **Propafenone** does not block potassium channels.

Pharmaco Kinetics

- **Flecainide** is absorbed orally and is metabolized by CYP2D6, eliminated renally and dosage adjustment may be required in renal disease.
- **Propafenone** is metabolized to active metabolites primarily via CYP2D6, and also by CYP1A2 and CYP3A4. The metabolites are excreted in the urine and the feces.

Therapeutic Uses

- **Flecainide**;
    - **Atrial fibrillation/flutter conversion**: 300 mg orally once.
    - **Atrial fibrillation/flutter maintenance**,
    - **Ventricular tachycardia**,
    - **Wolff-Parkinson-White Syndrome**,
    - **Supraventricular tachycardia**.
        - 50-150 mg orally/12 h.
- **Propafenone**;
    - **Atrial fibrillation/flutter conversion**: 600 mg orally once.
    - **Atrial fibrillation/flutter maintenance**,
    - **Ventricular tachycardia**,
    - **Wolff-Parkinson-White Syndrome**,
        - *Immediate release*: 150-300 mg orally every 8-12 hours.
        - *Extended release*: 225-425 mg orally every 12 hours.

Side Effects

- **Flecainide**; ***common side effects***; blurred vision, dizziness, and nausea.
- **Propafenone**; has a similar side effect, but it may also cause **bronchospasm** due to its β-blocking effects, it should be avoided in patients with asthma.
- Both drugs should be used with caution with potent inhibitors of CYP2D6.

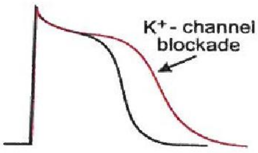
2) Class II (β-blockers)

Propranolol (Inderal®)	**Metoprolol** (Lopressor®)	**Atenolol** (Tenormin®)
Bisoprolol (Concor®)	**Esmolol** (Brevibloc®)	

- Antiarrhythmic effects of these drugs are not fully known.
- These drugs diminish phase 4 depolarization and, thus, ***depress*** **automaticity**, ***prolong*** **AV conduction**, and ***decrease*** **heart rate** and **contractility**.
- Class II agents are ***useful in treating*** **tachyarrhythmias** caused by increased sympathetic activity.
- They are also ***used for*** **atrial flutter** and **fibrillation** and for **AV nodal reentrant tachycardia**. In addition, β-blockers ***prevent*** **life-threatening ventricular arrhythmias following a myocardial infarction**.
- **Esmolol** is a short acting β-blocker used primarily as an ***antiarrhythmic drug for*** **intraoperative and other acute arrhythmias**.
- **Sotalol** is a nonselective β-blocker that prolongs the action potential ⇨ **class III action**.

Recent Study; Botox® (Clostridium botulinum) might prevent irregular heartbeat (atrial fibrillation) after bypass surgery.

3) Class III (Potassium-Channel Blockers)



- Class III agents block potassium channels and, thus, diminish the outward potassium current during repolarization of cardiac cells.
- These agents ***prolong*** the **duration of the action potential *without* altering phase 0 of depolarization** *or* the **resting membrane potential** (prolong the effective refractory period, increasing refractoriness).

Amiodarone (Cordarone®)

- **Amiodarone** [a-MEE-oh-da-rone] is a member of a class of antiarrhythmic drugs with predominantly Class III effects.

Mechanism OF Action

- It has complex effects, showing class I, II, III, and IV actions, as well as α-blocking activity.
- Its **dominant effect** is ***prolongation*** of the **action potential duration** and the **refractory period** by blocking K^+ channels.

Pharmaco Kinetics

- ***Structure***; **Amiodarone *contains* iodine** and is related structurally to thyroxine.
- ***Bioavailability***; bioavailability = 35-65% (***due to*** variably absorption).
- ***Onset of action***; may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses.
- ***Elimination half-life***; is a complex, with a rapid component of 3-10 days (50% of the drug) and a slower component of several weeks.
- ***After discontinuation of the drug***; effect are maintained for 1-3 months. Measurable tissue levels may observed up to 1 year after discontinuation.
- ***Metabolism***; amiodarone is metabolized to des-ethyl-amiodarone (DEA) by the cytochrome P450 enzyme group CYP3A and CYP2C8. Dose should be reduced by up to 50% in substantial liver impairment
- ***Elimination***; biliary excretion.

Therapeutic Uses

- ***Dosage Guidelines for Amiodarone***;

Life-threatening arrhythmia	150-mg IV bolus over 10 minutes (if necessary, bolus may be repeated in 10 to 30 minutes); then 1 mg per minute for 6 hours; then 0.5 mg per minute for 18 hours; then reduce IV dosage or convert to oral dosing when possible.
Ventricular arrhythmia	800 to 1,600 mg per day in divided doses until a total of 10 g has been given; then 200 to 400 mg per day.
Atrial fibrillation	600 to 800 mg per day in divided doses until a total of 10 g has been given (may use higher initial dosage or IV dosing in unstable inpatients); then 200 mg per day.

Toxicity

- Amiodarone shows a variety of ***toxic effects*** including;
  - **Pulmonary fibrosis** 3-17%, **hyperthyroidism** 3%, **hypothyroidism** 30% (**amiodarone-induced thyrotoxicosis**; **AIT**), **neurologic toxicity** 20-40%, **GI upset**, **photosensitivity**, **hepatitis**, **blue-gray skin discoloration** 15%, **heart block** 14%, **hypotension** (IV) and **phlebitis** (IV).
- ***Most common drug interaction***; warfarin, digoxin, statins.
- ***Finally***; Keep an eye on amiodarone patients.

Dronedarone (Multaq®)

- **Dronedarone** [droe-NE-da-rone] is a ***non-iodinated*** benzofuran **amiodarone derivative**, it does not have the iodine moieties that are responsible for thyroid dysfunction associated with amiodarone.
- ***Pharmacokinetics***; ***less*** **lipophilic**, has ***lower*** **tissue accumulation** and has a ***shorter*** serum **half-life** than amiodarone.
- ***Mechanism***; ***like*** **amiodarone**, it has class I, II, III, and IV actions.
- ***Side effects***; Dronedarone has a ***better*** **adverse effect profile** than amiodarone ***but*** **may still cause liver failure**.

- ***Uses***; Dronedarone is used to maintain sinus rhythm in **atrial fibrillation** or **flutter**, ***but*** it is **less effective** than amiodarone.
- ***Dose***; 400 mg orally 2 times a day with a meal.
- ***FDA Warning***; Dronedarone is ***contraindicated*** in **patients with symptomatic heart failure with recent decompensation requiring hospitalization** or **NYHA class IV heart failure**.
- **Celivarone** is another ***non-iodinated*** benzofuran **amiodarone derivative** similar to dronedarone that is currently undergoing clinical trials (Sanofi-Aventis) for the prevention of ventricular recurrence.

Sotalol (Betacor®)

- **Sotalol** [SOE-ta-lol] is a ***non-selective*** **competitive β-adrenergic receptor blocker** that also exhibits **Class III antiarrhythmic properties**.
- The drug is formulated as a ***racemic mixture*** of D-(dextrorotatory) and L-(levorotatory) sotalol.
- The ***l*-sotalol** has **β-blocking activity**, and ***d*-sotalol** has **class III antiarrhythmic action**.
- ***Pharmacokinetics***;
  - ***Oral bioavailability*** of Sotalol is 90 to 100%, after oral administration, peak plasma concentrations are reached in 2.5 to 4 hours.
  - ***Metabolism***; Sotalol does not bind to plasma proteins and is not metabolized.
  - ***Excretion*** is predominantly by the kidneys in unchanged form with a half-life 12 hours.
- ***Uses***; used for maintenance of normal sinus rhythm in patients with **atrial fibrillation, atrial flutter**, or refractory paroxysmal supraventricular tachycardia and in the treatment of **ventricular arrhythmias**.
- ***Dose***;
  - ***Initial dose***: 80 mg orally 2 times a day, **dose *should be* adjusted** gradually every 3 days in order to attain steady state plasma concentrations and allow for monitoring of QT intervals.
  - **Dose should be *adjusted*** in people with a creatinine clearance rate below 40 mL/min.
- ***Side effects***; This drug can cause the typical **adverse effects *associated*** with **β-blockers *but*** has a ***low rate*** of **adverse effects *when compared*** to **other antiarrhythmic agents**.

Dofetilide (Tikosyn®)

- **Dofetilide** [doh-FET-il-ide] is a pure potassium channel blocker.
- ***Pharmacokinetics***; It is **100% bioavailable**, **Verapamil** ***increases*** **peak plasma dofetilide concentration** by increasing intestinal blood flow. Approximately 80% excreted in urine of which approximately 80% is unchanged drug, ***dose***; 125-500 mcg twice a day.
- ***Uses***; It is approved for the maintenance of normal sinus rhythm in patients with **atrial fibrillation**.
- ***Because*** of the **risk of pro-arrhythmia, treatment with Dofetilide** ***should be initiated*** **in hospital** ***after baseline measurement*** of the **rate corrected QT interval** (QT c) and **serum electrolytes**.
- ***Drug interactions***; Inhibitors of the renal cation secretion mechanism, e.g. cimetidine, ketoconazole, verapamil, trimethoprim, prochlorperazine and megestrol.

Ibutilide (Corvert®)

- **Ibutilide** [eye-BYOO-tih-lide] is a **potassium channel blocker *that also have* action on the slow sodium channel** (**mixed class III and IA action**).
- ***Pharmacokinetics***; It is ***available*** in **intravenous infusion** ***only***.
  - ***After*** IV administration, ibutilide is ***rapidly*** **cleared by hepatic metabolism.**
  - The metabolites are ***excreted*** **by the kidney**.
  - The ***elimination*** **half-life** averages **6 hours**.
- It is ***used*** for the **acute conversion of atrial flutter** and **atrial fibrillation** (more effective in atrial flutter than atrial fibrillation) to normal sinus rhythm.
- ***Because*** of the **risk of pro-arrhythmia, treatment with Ibutilide** ***should be initiated*** **in hospital** ***after baseline measurement*** of the **rate corrected QT interval** (QT c).

Vernakalant (Brinavess®)

- **Vernakalant** is a **multi-ion channel blocker** that was ***developed for*** the treatment of **atrial fibrillation** (final approval for this purpose is pending).
- Vernakalant does not change the QT interval on the ECG.
- ***Side effects***; dysgeusia (disturbance of taste), sneezing, paresthesia, cough and hypotension.

4) Class IV (Calcium Channel Blockers)

Verapamil (Isoptin®) | Diltiazem (Altiazem®)

- **Class IV drugs** are the non-dihydropyridine calcium channel blockers **Verapamil** [ver-AP-a-mil] and **Diltiazem** [dil-TYE-a-zem].
- **Verapamil** shows ***greater action*** on the **heart *than*** on **vascular smooth muscle**, and **Diltiazem** is ***intermediate*** in its ***actions***.
- They also slow conduction in tissues that are dependent on calcium currents, such as the AV and SA nodes.
- These agents are ***more effective against*** **atrial than *against* ventricular arrhythmias**.
- *Uses*;
    - **Supraventricular tachycardia** is the ***major arrhythmia*** **indication** for **Verapamil**.
    - **Verapamil** can also ***reduce*** the **ventricular rate in atrial fibrillation and flutter**.
    - **Diltiazem appears** to be ***similar*** in **efficacy** to **Verapamil** in the management of **supraventricular arrhythmias**, including **rate control in atrial fibrillation**.

5) Miscellaneous Antiarrhythmic Agents

- Certain agents used for the treatment of arrhythmias do not fit the conventional class 1-4 organization. These include digitalis, adenosine, magnesium and potassium.

Digoxin (Lanoxin®)

- **Digoxin** inhibits the Na^+/K^+-ATPase pump, ***prolonging*** the **effective** ***refractory period*** and ***diminishing*** **conduction velocity** in the **AV node**.
- Digoxin is used to control **atrial fibrillation** and **flutter**.
- *Note*: Serum digoxin concentrations of 1-2 ng/mL are desirable for atrial fibrillation or flutter, whereas lower concentrations of 0.5 to 0.8 ng/mL are targeted for systolic heart failure.

Adenosine (Adenocard®)

- **Adenosine** [ah-DEN-oh-zeen] is a naturally occurring nucleoside, but ***at high doses***, the drug ***decreases*** **conduction velocity**, ***prolongs*** the **refractory period**, and ***decreases*** **automaticity in the AV node**.
- **IV adenosine** is the *drug of choice* for **acute supraventricular tachycardia**.
- **Adenosine** has an ***extremely*** **short duration of action** (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells.
- *Dose*; It is usually given in a **bolus** dose of **6 mg** ***followed***, if necessary, by a dose of **12 mg**.
- *Toxicity*; **flushing** (20%), **chest pain** (10%) and **hypotension**.

Magnesium Sulfate

- **Magnesium** is necessary for the transport of sodium, calcium and potassium across cell membranes.
- It ***slows*** the **rate of SA node impulse formation** and ***prolongs*** **conduction time**.
- IV magnesium sulfate ***used for*** patients with **digitalis-induced arrhythmias *who were* hypomagnesaemia**.
- The ***usual dosage*** is 1 g (as sulfate) given IV over 20 minutes and repeated once if necessary.

Surgery and Medical Devices

- **Medical devices:**
    - Pacemaker and implantable cardioverter-defibrillators (ICD).
- **Surgical treatments:**
    - ***Maze procedure;*** this involves making a series of surgical incisions in the upper half of the heart (atria).
    - ***Ventricular aneurysm surgery:*** In some cases, a bulge (aneurysm) in a blood vessel leading to the heart is the cause of an arrhythmia. It involves removing the aneurysm.
    - ***Coronary bypass surgery;*** if patient have severe coronary artery disease.